

Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma

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Twenty subjects (aged 6–20 years) with moderately severe bronchial asthma participated in an open controlled trial with intravenous immunoglobulin (IVIG) given as five monthly infusions with a mean dose of 0.8 g/kg body weight. A follow-up was performed 4 and 14 months after the treatment period. Nine of 14 children in the treatment group completed the trial. Two children experienced severe headache after the first infusion, another two patients were taken off the study for reasons unrelated to the IVIG therapy, and one patient dropped out from lack of motivation. In six of the IVIG-treated children, there was a reduction in the daily intake of inhaled steroids at an unchanged or reduced histamine reactivity. Of the remaining three children, two showed a reduction in bronchial hyperreactivity, but their steroid dose was not reduced. Six patients participated in a reference group to determine seasonal variations of symptoms. One of them improved during the study period, and the condition of the other five deteriorated, as indicated by increased medication without reduced histamine reactivity. After 14 months, there were no significant differences in clinical symptoms, nor in sensitivity to histamine between the treated patients and the controls, as the condition had improved also in the latter. We have thus been able to confirm, in a group larger than those in previously published reports, some clinical improvement of asthma by IVIG therapy at a lower dose than previously used and in children with only moderately severe disease. The effect was still present 4 months after the termination of IVIG therapy but not after 14 months. As the effects were small and temporary and the treatment is complicated and expensive, IVIG therapy cannot at present be recommended for general use. A double-blind, placebo-controlled study of the effect of IVIG in asthma is needed.

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Asthma is the most common chronic disease in childhood, affecting some 4–15% of children and adolescents (3). Oral steroids are effective, but long-term treatment with these drugs is associated with various adverse effects (1, 9, 11, 20). The use of inhaled corticosteroids (IS) therefore represents a major improvement in the treatment of children with asthma (9). In most studies, children and adolescents show no adverse effects from IS with doses of 200–400 µg/d (9, 11). However, in a recent study, Wolthers & Pedersen reported retarded bone growth, as measured by knemometry, after IS in doses from 800 µg/d (23). Hence, it seems to be important to keep IS at the lowest possible dose to prevent symp-

toms and progressive lung damage caused by inflammation and subsequent fibrosis.

Intravenous immunoglobulin (IVIG) is frequently used in various immunologically mediated diseases (reviewed in 8, 13). It has also been tried in asthma. Relatively low doses, i.e., about 200 µg/kg body weight, administered monthly, ameliorated asthma in patients with IgG subclass deficiencies (15). In asthmatic patients with normal humoral immunity, however, low-dose IVIG had no effect (19).

Mazer et al. recently reported that monthly infusion of 2 g IVIG/kg body weight improved the disease in patients with severe, disabling asthma. They succeeded in gradually reducing steroid doses in

most patients (12). We have assessed IVIG in children and adolescents with less severe asthma. Our reason for undertaking the study was concern with possible long-term effects of IS and with lung damage caused by the asthma. If IVIG has an immunomodulatory effect in asthma, it might be possible to reverse the inflammatory process in the airways and achieve long-lasting improvement at a lower steroid dose.

Material and methods

Patients

Seventy-four children and adolescents with chronic, long-term, persistent asthma classified as moderately severe or severe (grades 3–4 asthma; Table 1) despite medication with at least 400 µg IS/d were invited to participate in the study. The patients were between 6 and 20 years of age and registered in our catchment area. Twenty-five of them agreed to participate in the study. None of them had suffered life-threatening episodes of asthma. At clinical evaluation, five of the 25 asthmatic patients had improved since their last visit to the hospital and were excluded from the study. Of the remaining 20 patients, six declined treatment with IVIG.

All patients had had persistent asthma for 1–14 years (mean 6.5 years). They had taken IS for 1–5 years. Eighteen of them were skin-test-positive to at least one aeroallergen, or had elevated levels of either serum IgE or specific serum IgE, as determined by RAST. Except for their asthma and allergy, they were healthy. They required 400–2000 µg IS/d and inhaled β_2 -agonists as needed. Six of them also used cromolyn sodium (SCG) three to four times daily. A few patients also took oral β_2 -agonists and/or theophylline. Several attempts had been made over the past years to optimize the dose of IS in all patients. The pharmacotherapy had been reevaluated at every checkup to keep the patient almost free from symptoms, i.e., with a need for inhaled β_2 -agonists not more than twice a week. Lung-function tests, including home monitoring of peak expiratory flow rate (PEFR) and spirometry with flow-volume curves,

had also been used to assess the state of health and to optimize treatment.

Study design

As this was a pilot study to test the feasibility and potential effects and side-effects of IVIG therapy in moderately severe asthma during childhood and adolescence, the study was open and the families could choose which group to join. Patients who were willing to participate in the study but who refused IVIG treatment served as a reference group to assess seasonal variations in lung function and skin tests. It was not acceptable to randomize the patients to treatment and control groups, or to give placebo infusions, and it was impossible to have a completely blinded evaluation. We therefore chose to use the reference group as our "control group" to assess seasonal variations among the patients.

During the treatment period with IVIG, five infusions were administered every 4 weeks (mean 28 ± 3 d) (Table 2). A follow-up was done 4–5 months and 14 months after the treatment period. The control group participated in all the procedures, except the intravenous infusions.

Home assessment

The patients kept diaries in which asthma symptoms, PEFR values, and the use of inhaled β_2 -agonists were recorded twice daily. The patients (and their parents) were instructed to score the symptoms of asthma (cough, breathlessness, diminished physical fitness, wheezing, mucus, awakening caused by asthma) as they occurred, according to a 6-point scale (Table 3).

The number of doses of β_2 -agonists (dry powder or aerosol) taken daily or nightly was reported in the diaries and later transformed into a 5-point scale (Table 3).

PEFR was measured twice daily with a hand-held mini-Wright peak-flow meter before inhaled medication was taken. If a β_2 -agonist was needed, the measurement was repeated 10 min after inhalation.

Table 1. Classification of severity of asthma according to Swedish Paediatric Allergy Society

Grade	Days of decreased activity or disturbed sleep/month despite present medication
1. Minor, occasional asthma	0*
2. Slight asthma	1–2
3. Moderate asthma	3–6
4. Severe asthma	> 6
5. Very severe asthma	Chronic disabling asthma or life-threatening attacks

* Includes patients with asthma connected only to extreme physical activity and/or symptoms when exposed to relevant allergen for only short period.

Table 2. Study protocol: controls participated in all procedures except gamma globulin infusions

		IVIG infusions						
		1	2	3	4	5		
	1991	Feb.	March	April	May	June	July	Nov.
Serum sample		X	X	X	X	X	X	X
IgG subclass		X			X			X
Histamine threshold		X			X			X
Skin prick test		X			X			X
Pulmonary function		X	X	X	X	X	X	X

Table 3. Scoring of restricted activity and medication. "Work" = go to school or work. Intake of β_2 -agonists was recorded as the number of inhaled doses per 24 h. PEFR scores were obtained by measuring % of predicted value (% pred.) and % variability of PEF (% var.) over day. If scores derived from predicted values and variability did not agree, mean of two was used. Total daily dose of inhaled steroids (IS) is given as $\mu\text{g}/\text{d}$

Score	Daytime	Nighttime	β_2 -Agonists	PEFR % pred./% var.	IS
0	Unrestricted activity	No symptoms	0	> 100; 0	0
1	One short period of minor symptoms	Minor symptoms when awake	1	> 93; < 3	-200
2	Two short periods of minor symptoms	Awake once because of asthma	2-3	> 87; < 6	-400
3	Symptoms during day but unrestricted activity	Awake twice because of asthma	4-6	> 81; < 12	-800
4	Symptoms most of day and restricted activity	Awake most of night because of symptoms	> 6	< 82; ≥ 12	> 800
5	Severe symptoms; cannot work	No sleep during night			

The best of three registrations was recorded in the diary. A PEFR score was established on the basis of the mean value in percentage of predicted PEFR for each patient (Table 3). Predicted values were calculated by Swedish reference values (21).

The PEFR variability was also taken into account, a range with $\pm 6\%$ from the mean of PEFR being used. The variability was calculated as percentage of PEFR reaching outside the range. The 12% range was selected to ensure that changes over time in PEFR variability could be seen (2, 18). Thus, PEFR scores were calculated as summarized in Table 3. If mean and variability differed, the mean of the two was used.

From the information in the diaries, a weighted total score was calculated according to a modification of the "total asthma score" described earlier (4). This was done by adding the day- and nighttime symptom scores (0-5; $\times 0.6$), PEFR scores (0-4; $\times 0.75$), the scores for inhaled β_2 -agonists (0-4; $\times 0.75$) and IS (0-4; $\times 1$), and the use of SCG or oral β_2 -agonists and theophylline (1 point each). Thus, the maximum total score was 15. A mean monthly score was calculated. A reduction of the total score by 50%, comparing a period of 1 month in the beginning and at the end of the study, was chosen as a clinically relevant improvement, one necessary to justify treatment with IVIG in the future.

Office assessment

Diaries were scrutinized monthly and completed, if necessary, by one of us (TJ). On the basis of physical examination, diaries, and pulmonary function tests, the minimum dose of steroids for the following month was determined at each visit.

Dynamic spirometry, including FEV₁ (forced expiratory volume in 1 s) and MEF₅₀ (maximal expiratory flow at half of the vital capacity), was performed on each visit before and after inhalation of β_2 -agonists (reversibility test), with a dry-sealed spirometer (Vicatest 5[®], Mijnhardts, The Netherlands). The best of three values was used for comparisons.

Bronchial histamine provocations (BHP) were performed three times in each patient during the study, i.e., before the treatment period, at the fourth visit, and at the follow-up visit. The BHP was not done if the FEV₁ was below 70% of predicted value unless the FEV₁ had been stable at that lower level for several months. After checking that the FEV₁ was stable within 5%, the patients inhaled saline for 2 min via a jet nebulizer (Aiolos[®], Medicinsk Teknik AB, Karlstad, Sweden), and the FEV₁ recorded was used as base line. Histamine chloride solution (10 mg/ml) was then inhaled by 2-min tidal volume breathing at 5-min intervals with a SPIRA[®] Elektro 2 inhalation dosimeter (Respiratory Care Centre, Finland). Inhalation started at a concentration of 0.03 mg/ml and increased by fourfold increments up to 8 mg/ml or until a fall in FEV₁ of at least 20% was recorded. The cumulative histamine dose for 20% reduction of FEV₁ from base line was then calculated (PD₂₀Hi).

Skin tests were performed as prick tests (SPTs) with commercial extracts (Soluprick[®] Aquagen, 10 HEP, ALK, Hørsholm, Denmark) of 10 common aeroallergens (dog, cat, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, *D. farinae*, *Cladosporium*, and *Alternaria*). Histamine hydrochloride (10 mg/ml) served as a positive control, and albumin diluent as a negative control. The SPTs were done three times, i.e., on the same occasions as the BHP. All tests were performed in duplicate, and no antihistamines were allowed during the preceding 72 h. Wheals were outlined after 15 min with a felt-tip pen, and test results were transferred by transparent tape to a record for later comparison of wheal sizes. Wheal sizes were calculated as the mean of the largest diameter and the diameter perpendicular to it.

At each visit, blood was drawn, and the serum was frozen within 60 min at -70°C for later analysis. Serum IgE was analyzed with the Pharmacia CAP[®] system in accordance with the instructions of the manufacturer (Pharmacia, Uppsala, Sweden), and serum IgG was analyzed by immune nephelometry (Behring Nephelometer Analyser[®]). The

IgG subclasses 1-4 were analyzed by a modified Mancini method (7). Anti-IgE antibodies of IgG isotype were quantitated by a modified ELISA (22).

For quantitation of eosinophils, peripheral blood samples were diluted 1/20 with a solution of 0.019% Magdala red in 0.7% Na₂CO₃ and 11.65% acetone. The cell suspensions were gently agitated for 2 min and counted at $\times 400$ magnification in a Fuchs-Rosenthal hemocytometer. Eosinophil cationic protein (ECP) (17) and tryptase (6) were analyzed by radioimmunoassay. Liver transaminases were analyzed by photometry according to ICC. IgG, transaminases, and eosinophils were analyzed on the day of blood sampling, and the other tests were performed at the end of the study.

Immunoglobulin infusion

According to the initial protocol, IVIG (Gammagard, Baxter), 1 g/kg body weight, was to be given as a 5% solution every 4 weeks for 5 months. However, 11 of the 12 first treated patients experienced headache, starting about 20 h after the first infusion and lasting for an average of 17 h. Several attempts were made to prevent the headache. Prophylactically administered diphenhydramine, paracetamol, furosemide, and NSAIDs had no effect. A 10% solution, to reduce the volume of i.v. fluid, was tried, but this procedure also failed to prevent the headache. On the assumption that the headache was caused by antigen-antibody complex formation and was related to the high dose used, the last two patients in the first series were given 0.5 g/kg body weight IVIG as a 10% solution. These patients ex-

perienced only minor headache. The protocol was therefore modified, and the patients received 0.5 g/kg as the second infusion. The doses were then gradually increased in subsequent infusions back to 1 g/kg. This procedure produced no side-effect of postinfusion headache. The mean dose given was 0.8 g/kg. Most patients, as well as all the nurses, preferred the more rapid infusion made possible with the 10% solution. Shivering and fever up to 38.6°C, lasting for 3-5 h, were recorded after seven of the 36 infusions with 10% solution. Two patients experienced local pain at the infusion site at this concentration and continued to receive IVIG as a 5% solution.

Ethics

The study was conducted in accordance with the Helsinki Declaration and approved by the Human Research Ethics Committee at the University Hospital, Linköping, Sweden, and the Swedish Medical Products Agency.

Statistical analysis

For statistical analysis, the Mann-Whitney U-test and rank sum test were used in calculating inhaled steroids, total IgE levels, and the total score. Differences resulting in a *P*-value of less than 0.05 were considered to be significant.

Results

In the treatment group, 9/14 children completed the trial (Table 4). Two children declined further IVIG

Table 4. Total score: symptoms, PEFR, inhaled β_2 -agonists (β_2), inhaled steroids (IS), cromolyn sodium (SCG), oral β_2 -agonists or theophylline. Values presented are for each item mean of 1 month before treatment (beginning) and 4 months after the last infusion (end). Patients who failed to complete diaries were not included in statistical calculation

Scores	IVIG group									Control-group					
	HA	JW	HH	AC	PB	ST	HF	MK	RJ	MF	EK	JA	JC	KN	RA
Symptoms	0.4	0	—	0.6	0.6	0.1	0.3	0.1	—	0.2	0.2	0.5	0	—	—
	0.2	0	—	0.5	0.3	0.2	0.5	0	—	0	0	0.7	0.5	—	—
PEFR	2.2	0	—	2.2	1.5	0.8	1.5	0.8	—	1.5	2.2	2.2	1.9	—	—
	1.5	1.1	—	1.5	1.9	0.4	1.5	0	—	1.5	2.6	1.9	2.6	—	—
β_2	1.5	0	—	0.6	0.3	1.5	2.2	0.5	—	2.2	1.6	3	0	—	—
	0.3	0.2	—	0.5	0.1	0.2	2.1	0.1	—	1.1	0.7	2.4	0.4	—	—
IS	4	4	4	4	4	3	3	2	2	2	2	4	4	2	2
	2	0	4	2	2	2	4	0	3	4	4	4	1	4	3
SCG	0	1	1	0	0	0	1	0	0	0	0	0	1	1	0
	0	1	1	0	0	0	1	0	0	1	1	1	1	1	0
Oral β_2 or theophylline	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Total															
Beginning:	9.1	5.0	(5)	8.4	6.4	5.4	8.0	3.4	(2)	5.9	6.0	10.7	6.9	(3)	(2)
End:	4.0	2.3	(5)	4.5	4.3	2.8	9.1	0.1	(3)	7.6	8.3	11.0	5.5	(5)	(3)

after the first infusion because of severe postinfusion headache. Another two patients were taken off the study for reasons unrelated to the IVIG therapy (one girl became pregnant, and the mother of one child developed a severe disease and could therefore not help her child to participate in the study), and one patient dropped out from lack of motivation.

The daily and nightly symptom scores were similar in the treated patients and the open controls, both in the beginning and at the end of the study. In the IVIG group, the mean scores were 0.48 (range 0–0.93) during the first month and 0.42 (0.06–0.89) between the sixth visit and the follow-up visit. In the reference group, the corresponding figures were 0.37 (range 0–0.76) and 0.50 (0–1.15). The scores based on the use of β_2 -agonists decreased during the study in both groups, indicating that this decrease could have been due to a seasonal variation.

In both groups the FEV₁ values and the mean PEFR values were similar, i.e., about 100% of predicted values. Similarly, the variability remained constant over the treatment period.

Total scores were obtained from seven patients in the IVIG group and four controls. Two patients in each group failed to complete the diaries and were therefore not included in the calculations. At the end of the study period, there was a 46% (mean) reduction of total score in the IVIG group in all but one patient. In the reference group there was a mean increase in total score of 12% ($P < 0.05$) (Table 4).

In six of the nine actively treated children, the dose of IS was reduced from 720 (range 400–800) to 200 μg daily (range 0–400) (Fig. 1). This level was maintained for at least 4 months after the last infusion. Three children did not reduce their use of IS. Two of them continued with the same dose of IS, although they both had a reduced sensitivity to histamine, as shown by at least a fourfold increase in their PD₂₀Hi level. The third child's condition deteriorated during the infusion period, the IS being increased from 670 μg daily during the run-in period to 1200 μg daily at the end of the study period. This child had had a dog for 1 year and showed an increasing sensitivity to dog allergen in the repeated skin prick tests. The PD₂₀Hi remained unchanged during the study, but his variability in PEFR increased from 21% to 37%, and the mean of the PEFR values decreased by 5%.

In the reference group, five children increased their doses of IS by a mean of 380 μg (range 80–770) daily, i.e., from 520 (mean) to 900 μg daily. One girl reduced her daily IS from 800 to 200 μg . However, her PD₂₀Hi-level decreased, as indicated by a 50% lower level at the end of the study. Her variability in PEFR increased from 8% to 42%, and the mean of the PEFR values decreased by 5% (Fig. 2).

Systemic or oral steroids were administered to

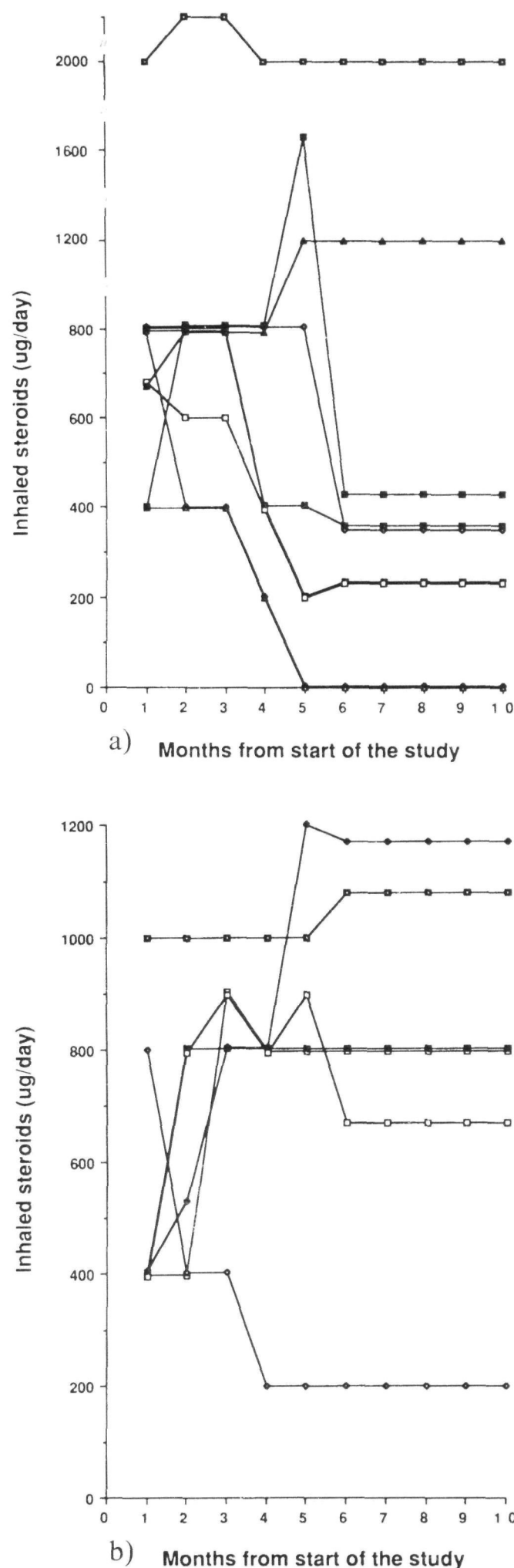


Fig. 1. Average daily dose of inhaled steroids during study period. Each line represents single patient. a) IVIG group ($n = 9$); b) open controls ($n = 6$).

two children with acute exacerbations, i.e., one patient in each group. They had both accidentally

ingested a cake containing nuts, to which they were allergic. Both boys reacted with asthma symptoms, and they therefore were given a single injection of 100 mg hydrocortisone as well as 6 mg oral beta-methasone. SCG was used by three patients in the IVIG group at an unchanged dose during the trial. Two of the controls used SCG when entering the study, and three started SCG at the fourth and fifth visits because of seasonal worsening of their asthma.

At the second follow-up after 14 months, the medication was similar in the IVIG patients and the reference group. This was due to a reduced medication in the latter and to clinical improvement in both groups.

The tolerance to histamine increased in the IVIG group from a mean dose of 330 μ g (range 40–1100) to 1230 μ g (range 150–2530). The histamine sensitivity remained unchanged in the reference group, with mean values of 700 μ g (range 15–2475) before and 670 μ g (range 15–1960) after the treatment period. At the second follow-up after 14 months, however, the sensitivity to histamine was similar in the two groups, as the patients not receiving IVIG had improved to the same extent as the IVIG-treated subjects.

Of the nine patients who completed the IVIG infusions, six had at least one positive SPT at the start of the study. During the study period, there was a 12% mean increase of the SPT wheals to allergens and a 7% mean increase to histamine (nonsignificant). In the reference group, five patients had positive SPTs to one or more antigens. There was a 16% mean increase in allergen wheals during the study period, and a 2% mean decrease in histamine wheals.

No hematologic abnormalities were recorded in either group, either before or after the treatment period (data not shown). The mean serum IgG level was 11.6 g/l (range 8.3–15.1) before the first infusion, 14.0 g/l (10.8–20.0) before the third infusion, and 11.4 g/l (7.9–15.6) 4 months after the last infusion. The IgG subclass distribution did not change significantly during the study period.

In the IVIG group, the IgE levels tended to be lower after the treatment period than before it (median 336 kU/l, range 19–1848 before and 183 kU/l, range 17–1651 4 months after treatment). However, the difference was not statistically significant. Similarly, the IgE levels did not change significantly in the reference group over the study period, although there was a tendency toward increased levels, i.e., 499 (17–3033) kU/l and 656 (45–3055) kU/l.

The levels of IgG anti-IgE antibodies, eosinophil counts, and the levels of ECP did not change sig-

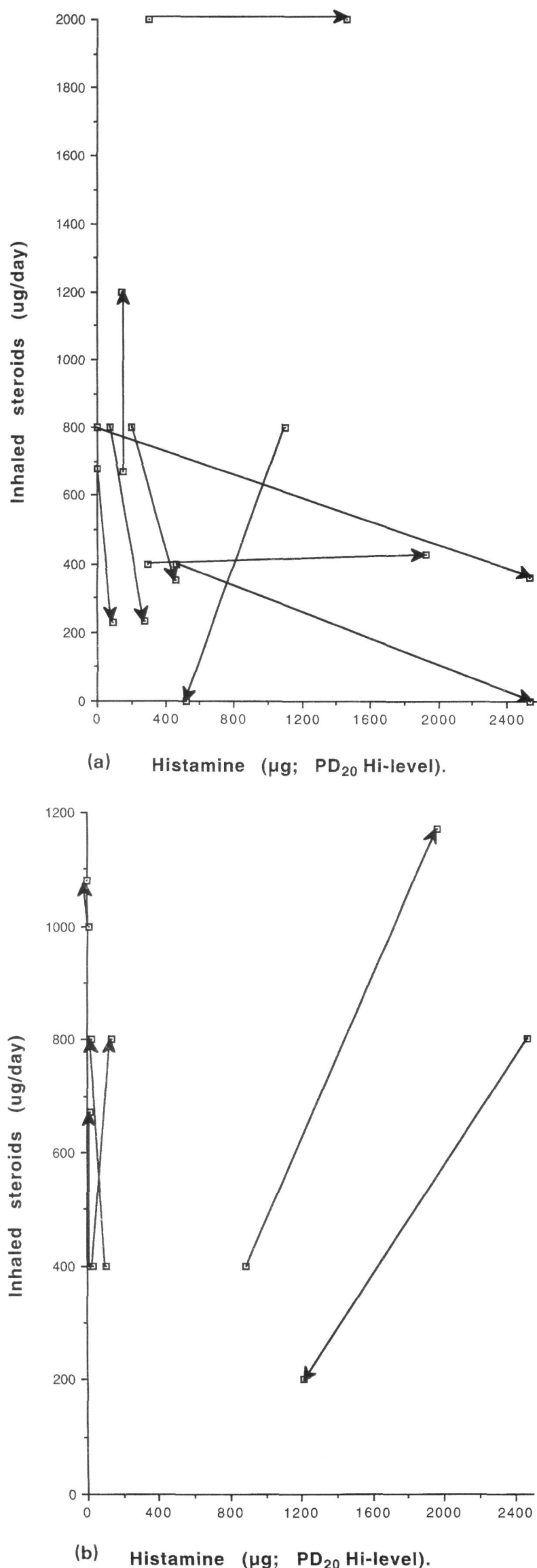


Fig. 2. Individual histamine thresholds and daily use of inhaled steroids before and after IVIG therapy (a) and among open controls (b).

nificantly during the study period in either group (data not shown). All the tryptase levels were below detectable level, i.e., $<0.5 \mu\text{g/l}$.

Discussion

This study supports a previous report that IVIG may reduce clinical symptoms and the need for other medication in asthmatic children (12). The treatment seems to have some effect even in subjects with moderately severe asthma who do not need daily oral steroid medication. We could reduce the daily use of IS in six of the nine patients who completed the study with a concomitant reduction in bronchial hyperreactivity. In two of the remaining patients, there was a more than fourfold reduction in sensitivity to histamine. The only patient who did not improve showed an increasing sensitivity to dog allergen, and he had a dog at home. It is likely that his clinical condition deteriorated steadily over the study period because of increasing sensitivity and continuous exposure to allergens. After 14 months, however, no differences were discernible between those patients who had been treated with IVIG and those who had not. Any beneficial effect thus seemed to be temporary.

However, our results are less encouraging than those reported by Mazer et al. (12). In contrast to the patients in our study, the mean serum IgG level in their patients was approximately 5.8 g/l, i.e., a level below normal. The improvement attributed by them to the IVIG therapy may have been due to improved defense against infectious agents and consequently less exacerbation of asthma. This possibility is supported by an earlier report that IVIG therapy improved asthma in immunologically deficient patients with a serum IgG level around 3.5 g/l (15).

Mazer et al. administered monthly doses of 2 g/kg body weight IVIG, given as 1 g/kg on two consecutive days (12). The total cost of such treatment, i.e., for staff, immunoglobulin, and travel, was considered to be unacceptable. Furthermore, we expected the compliance to be lower with a regimen requiring more frequent visits to the hospital. For all these reasons, a lower dose was chosen, i.e., 1 g/kg. Despite this, all the patients complained of postinfusion headache. By reducing the amount of intravenously given fluid, lowering the doses to 0.5 g/kg, and then gradually increasing the doses again, this side-effect was overcome. The cause of the headache remains unknown. Very recently, it was reported that administration of IVIG can be associated with acute aseptic meningitis (16). Although we did not analyze the spinal fluid, our patients had no other indication of aseptic meningitis; e.g., neck stiffness. The initial headache was possibly due to formation of antigen-

antibody complexes. However, the search for IgG anti-IgE did not elucidate this question.

The mechanisms behind a beneficial effect of IVIG on asthma and the modes of action of IVIG in immunologically mediated diseases are unknown. Suggested mechanisms include Fc-receptor blockade of phagocytes, regulation of the idiotypic network, and interaction with cytokines (5, 10, 14). There were, however, no significant changes in the levels of IgG anti-IgE autoantibodies in the treated patients, as compared with controls. This suggests that the observed decrease in IgE levels did not occur secondarily to a change in the IgG anti-IgE antibody levels. We also monitored IgG over the study period to exclude the possibility that the administration of IVIG was associated with a depression of the endogenous IgG synthesis.

In conclusion, IVIG appears to reduce temporarily the severity of asthma. A randomized study in a larger group of patients with moderate and severe asthma is warranted, and the long-term effects should be further studied to define more precisely the clinical usefulness of this therapy, particularly in comparison with intensive conventional therapy.

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