

Effects of Long-Term Treatment with Low Dose Cimetidine on Allergen-Induced Airway Responses and Selected Immunological Parameters in Atopic Asthmatics

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Twenty asymptomatic atopic asthmatics were treated with either cimetidine 100 mg orally (13 patients) or placebo (7 patients) once a day for 4 weeks. Bronchial challenges were performed with the pertinent allergen immediately before and 2 and 4 weeks after the initiation of treatment and, finally, 4 weeks after the cessation of treatment. Before each challenge blood was drawn for the determination of specific IgE antibody levels (RAST procedure) and total IgE (PRIST), allergen- and anti-IgE-induced basophil histamine release, and mitogen-induced lymphocyte (³H)-thymidine incorporation. Patients treated with cimetidine were found to be significantly ($P < 0.05$) less responsive to bronchial allergen challenge during the treatment than before it; patients treated with placebo were more reactive ($P < 0.05$) 14 days after the initiation of treatment. The difference in responsiveness to treatment between the placebo and the cimetidine groups was significant 14 days ($P < 0.01$) and 4 weeks ($P < 0.05$) after the initiation of treatment; no significant difference in allergen responsiveness was recorded between the groups 1 month after cessation of treatment. No clear-cut changes in specific IgE antibody or total IgE levels, histamine release capacity, or mitogen-induced lymphocyte responsiveness were observed in either group, except that lymphocytes from cimetidine-treated patients tended to show an increased ratio of PHA- to PMA-induced thymidine incorporation. Thus, it was found that the treatment of asymptomatic atopic asthmatics with low-dose cimetidine reduced their allergen sensitivity in bronchial provocation tests by a mechanism which remains to be elucidated.

Key words: atopic asthma; basophil histamine release; bronchial allergen challenge; cimetidine; PRIST; RAST; ³H thymidine incorporation.

Accepted for publication 1 October 1984

Locally administered histamine induces bronchoconstriction in man. Moreover, patients with asthma react more strongly to histamine than do normal individuals. This effect of histamine is inhibited by histamine H₁-blockers (for review of subject see ref. 53). The H₂-blocker cimetidine has no effect or else it augments the response, but apparently only in asthmatics (10, 20, 22, 34, 44, 53).

Histamine is released from mast cells in the lung and from basophilic leukocytes by a specific antigen in reagin-mediated reactions. Thus, histamine is a potential mediator of asthma. Results obtained with human basophilic leukocytes *in vitro* suggest that histamine may regulate its own release by a feedback inhibition via H₂-receptor stimulation (17, 49). Moreover, an acute feedback inhibitory effect

of histamine on allergen-induced histamine release in human skin *in vivo* was recently demonstrated by Ting et al. (47, 48). Thus, H₂-receptor stimulation may inhibit the release of histamine (and even other mediators). The treatment of asthmatics with H₂-antagonist(s) may then be expected to aggravate antigen-induced bronchoconstriction. However, feedback inhibition by H₂-agonists is evidently not demonstrable with human lung mast cells *in vitro* (15, 25, 27, 48). In accordance with this, cimetidine (an H₂-blocker) does not seem to augment antigen-induced bronchial reactions (19, 44) or naturally occurring or exercise-induced asthma (16); rather Eiser et al. (10) reported inhibition of allergen-induced bronchospasms by intravenous cimetidine. Thus, the functional significance of H₂-receptors in human airways seems to be of minor importance in provocation tests of asthmatics with histamine or allergen (53).

The clinical efficacy of H₁-blockers in asthma is at best poor (53). We are not aware of any studies of the effect of long-term treatment of asthmatics with histamine H₂-antagonists. Such

studies would be of interest since histamine apparently affects immune responses (for review see 5).

It has previously been shown that a 3-week treatment of suitably sensitized guinea-pigs (1) or rats (Bergstrand et al., unpublished) with the H₂-agonist dimaprit or a low dose of cimetidine (1 mg/kg) – but apparently not with a higher dose of cimetidine – may reduce their anaphylactic response capacity *in vivo* and *in vitro*. This effect may be seen even 1 week after the cessation of treatment; the underlying mechanisms have not been clarified. We report here the results of a study concerning the effect of long-term treatment with low-dose oral cimetidine on the responsiveness of asthmatic subjects to bronchial allergen challenge.

MATERIAL AND METHODS

Twenty patients with extrinsic bronchial asthma (13 females and 7 males, mean age 30 years (range 21–46 years)) were included in the study. One further patient entering the study did not complete it. All had allergic asthma based on a

Table 1
Clinical data of patients admitted to study

Patient	Sex	Age	Diagnosis	Allergen	Prick-test	RAST
1	F	32	asthma	cat	+++	3
2	F	39	asthma	cat	+++	3
3	F	31	asthma	birch	+++	3
4	M	22	asthma	horse	+++	1
5	F	34	asthma	guinea pig	++++	0
6	F	22	asthma	horse	+++	2
7	M	34	asthma	cat	+++	4
8	M	23	asthma	cat	+++	2
9	F	22	asthma	horse	++++	2
10	F	25	asthma	horse	++++	4
11	F	27	asthma	horse	++++	4
12	M	39	asthma	rabbit	++	2
14	F	22	asthma	cat	+++	4
15	F	25	asthma	cat	+++	2
16	F	34	asthma	cat	++++	2
17	F	36	asthma	cat	+++	2
18	F	21	asthma	cat	++++	4
19	F	46	asthma	cat	+++	4
20	M	39	asthma	rabbit	++	2
21	F	23	asthma	cat	++++	2

history of allergy, a positive skin test, a positive RAST and a positive bronchial allergen provocation test (Table 1). None of the patients had had a respiratory infection during the preceding month and none had been exposed to the relevant allergens during the preceding 24 h. In the same period they had also avoided exercise. Before the start of the study, all patients were subjectively and objectively free from asthma symptoms and they had FEV₁ values within normal range. All patients were familiar with the inhalation and measurement procedures and had previously participated in similar studies.

Inhaled β -stimulating drugs were taken occasionally by some of the patients, but not less than 12 h before each test. None of the patients took methyl xanthines and none received immunotherapy. Smoking was not allowed for 4 h before the challenge or during it.

The study was designed as a double-blind comparison with parallel groups, between low-dose cimetidine (100 mg) and placebo once daily during a 4-week treatment period. Thirteen randomly selected patients received cimetidine and seven placebo (a 2:1 relation). This grouping was considered suitable with respect to the statistical analysis of the data.

Bronchial allergen challenge, specific and total IgE serum antibodies, allergen- and anti-IgE-induced basophil histamine release and mitogen-induced lymphocyte thymidine incorporation were determined before and 2 and 4 weeks after the initiation of treatment and 1 month after the cessation of treatment (Fig. 1). Blood samples were drawn approximately 15 min before allergen provocation tests. Each provocation test was performed at the same time of the day. For each individual, the same batch of specific allergen was used throughout the study in both the bronchial challenge and basophil histamine release tests.

Allergen-induced bronchial challenge

Allergen extracts were inhaled by the patients during 2 min with tidal breathing at 15-min intervals. The allergen solutions were administered by a Pari Inhaler Boy nebulizer (Paul Ritsau Pari-Werk GmbH and Co., Starnberg,

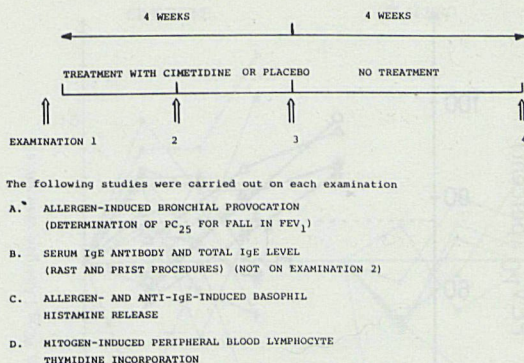


Fig. 1. Study design.

Germany; airflow 15 l/min, particle size 0.5–5.5 μ m and nebulizer output 0.75 ml/min, of continuous nebulization). Lung function measurements (FEV₁) were performed with a Monaghan M 403 Spirometer (Monaghan Corp., Denver, USA) immediately and 5, 10 and 15 min after each allergen inhalation. In the case of a more than 25% fall in FEV₁, the measurements were continued up to 30 min. After that patients were given an inhalation of a β_2 -stimulating agent, when necessary.

Before the initiation of treatment, the dose of the pertinent allergen causing a 25% reduction in FEV₁ was determined in each individual. The allergen concentration in the nebulizer reservoir was doubled at 15-min intervals until the patient showed the predetermined reduction in FEV₁. Since different allergen preparations with widely varying effective concentrations were used for different patients, the allergen doses inhaled are given in arbitrary units. Individual doses are expressed in a logarithmic scale; the lowest concentration of each allergen used was defined as one dose unit and each two-fold increase of allergen concentration corresponded to an increase of one dose unit. The allergen dose inducing a 25% reduction of FEV₁ was obtained by interpolation from plots of reduction in FEV₁ against the allergen dose. This interpolated dose of allergen, giving a 25% fall in FEV₁, was defined as the PC₂₅-value (Fig. 2). Exactly the same allergen concentrations were used and the same challenge procedure was followed for each patient on each examination. The change in PC₂₅ determined on ex-

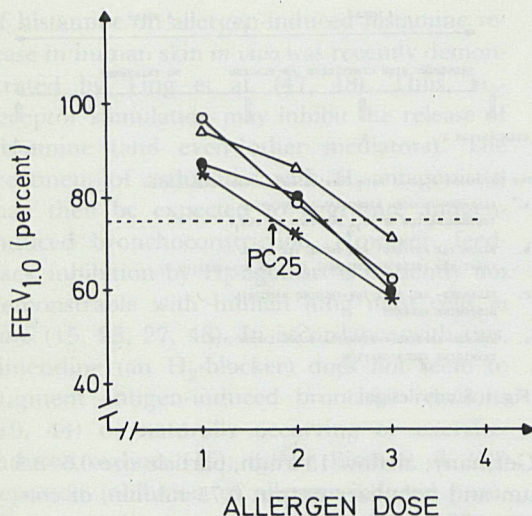


Fig. 2. Allergen provocation tests in patient No. 1 before initiation of treatment with cimetine (*), 2 (Δ) and 4 ($\circ$) weeks after initiation of treatment, and 1 month after cessation of treatment ($\bullet$). The figure shows the fall in $FEV_{1.0}$ (% of the initial value) as a function of the dose of the allergen plotted on a $\log_2$ scale.

aminations 2, 3, and 4 in relation to examination 1 were determined. These values were used for the calculations of the means and for statistical evaluation of the effects of treatment.

Specific IgE antibody and total IgE serum levels

Measurements were performed with the RAST and PRIST procedures using commercial kits obtained from Pharmacia, Uppsala, Sweden. The procedures recommended by the manufacturer were followed.

Allergen- and anti-IgE-induced histamine release from basophilic leukocytes

Blood was drawn into Vacutainer tubes containing EDTA as an anticoagulant. Because of the transportation times required, the blood was kept at approximately 2–4°C one day before the test was performed. The work of Radermecker (29) and pilot experiments of our own showed that there was no apparent difference in the release induced by allergen or by anti-IgE of

blood tested immediately or after storage in a refrigerator for 24 h. The day after blood harvest, the leukocytes were separated by sedimentation in a mixture of dextran-EDTA and glucose and washed twice in HEPES-A buffer, as described previously (6, 26). Following the reconstitution of leukocytes in the appropriate amounts of HEPES-ACM (HEPES-A buffer supplemented with Ca^{2+} and Mg^{2+}) (6), challenge was performed with allergen or anti-IgE in an appropriate dilution or vehicle. The release reaction was stopped after 40 min at 37°C by immersing the tubes in ice. Histamine was extracted and assayed spectrophotofluorometrically as described elsewhere (11, 26). Histamine release was expressed as a percentage of the total cellular histamine content after correction for spontaneous release. The antigen preparations used were of the same batch as that used for bronchial challenge experiments; anti-IgE was prepared as described elsewhere (26).

Mitogen-induced lymphocyte thymidine incorporation

^3H -thymidine incorporation of peripheral blood lymphocytes was determined following the incubation of monocyte-depleted mononuclear cell suspensions with phytohemagglutinin (PHA, Wellcome Laboratories, GB, 1 and 10 $\mu g/ml$), concanavalin A (Con A, Miles-Yeda, Rehovoth, Israel, 10, 20, 40 and 80 $\mu g/ml$), pokeweed mitogen (PWM, Pharmindustrial, Villeneuve, France, 1 and 10 $\mu g/ml$), phorbol myristate acetate (PMA, Sigma Chemical Co., St. Louis, MO., U.S.A., 0.5 $\mu g/ml$) or purified protein derivative (PPD, State Serum Institute, Copenhagen, Denmark, 2.5 $\mu g/ml$). Details of the experimental procedure have been reported previously (40).

Statistical methods

Wilcoxon's signed rank test was used to assess changes of PC_{25} within groups. Comparisons between groups were made using Wilcoxon's rank sum test.

The trial was approved by the Ethical Committee of the University of Gothenburg. Informed consent was obtained from all patients.

RESULTS

Allergen-induced bronchial challenge

Allergen-induced bronchial provocation tests were performed in each individual before the initiation of treatment with cimetidine or placebo (Challenge 1), after 2 weeks (Challenge 2), or 4 weeks (Challenge 3), and 1 month after the end of treatment (Challenge 4).

Cimetidine-treated individuals were found to need a higher allergen dose in challenges 2 and 3 than in challenge 1 to induce a reduction of the FEV_1 of more than 25% in 10/13 patients. This is exemplified by one patient in Fig. 2. Of the placebo-treated individuals 0/7 required a higher allergen dose and 2/7 required less allergen on examinations 2 and 3 than on examination 1 to respond.

The median PC_{25} -value recorded on examination 1 was slightly higher in the placebo-treated group (1.65) than in the cimetidine-treated group (1.45). The difference was not statistically significant. As treatment was randomized between individuals this difference merely reflects a chance variation in the dose of specific allergen chosen for the initiation of bronchial challenge.

Fig. 3A shows changes in PC_{25} -values (ΔPC_{25} -values) recorded on challenges 2, 3, and 4 relative to that determined in challenge 1 for each individual. Fig. 3B shows the means and the standard errors of the changes on each occasion. On examinations 2 and 3, cimetidine-treated individuals show significantly increased ΔPC_{25} values ($P < 0.05$) whereas placebo-treated individuals on challenge 2 show significantly ($P < 0.05$) decreased ΔPC_{25} values. The difference between the mean ΔPC_{25} of the two groups was significant on challenge 2 ($P < 0.01$) and on challenge 3 ($P < 0.05$).

Allergen-specific IgE antibody and total IgE serum levels

Table 2 shows that no significant change in either the allergen-specific IgE antibody or the total IgE level was recorded during or after treatment with cimetidine or placebo.

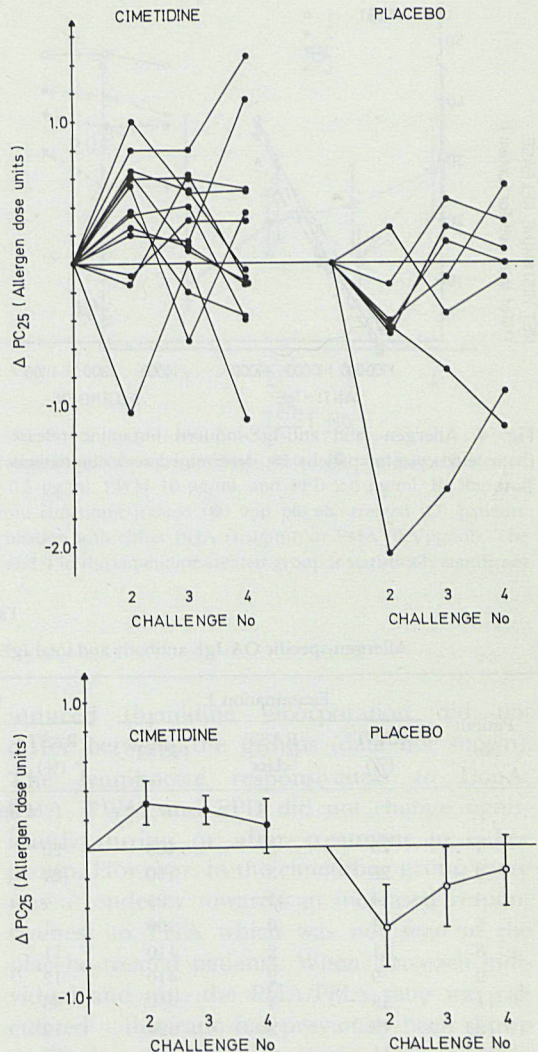


Fig. 3. A: Changes in PC_{25} (ΔPC_{25}) recorded on examinations 2, 3, and 4 relative to the PC_{25} value recorded on examination 1 for each individual. B: Mean $\Delta PC_{25} \pm SEM$ on each examination for cimetidine-treated and placebo-treated patients.

Allergen- and anti-IgE-induced histamine release from basophilic leukocytes

Concentration-response curves for histamine release were constructed at each test, using three concentrations of allergen and anti-IgE, respectively. Fig. 4 shows the data recorded for one individual patient in the cimetidine treatment group. In this patient the anti-IgE-in-

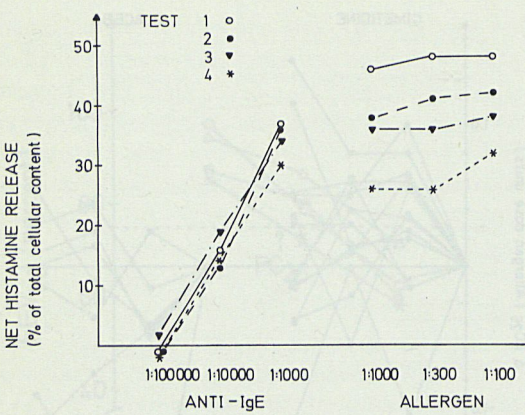


Fig. 4. Allergen- and anti-IgE-induced histamine release from leukocytes of patient 16, determined on examinations 1–4.

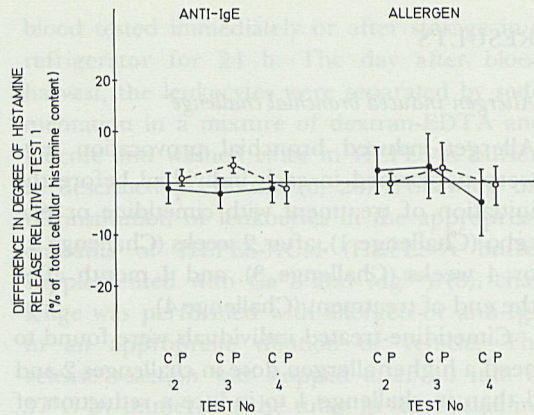


Fig. 5. Mean $\pm$ SEM changes in the degree of histamine release in cimetidine-treated (C) and placebo-treated (P) groups. For each individual, the change in the degree of release from that recorded on examination 1 was calculated for the results recorded on examinations 2, 3, and 4, as described in the text.

Table 2
Allergen-specific OA-IgE antibody and total IgE serum levels recorded on examinations 1, 3, and 4

Patient No.	Examination 1			Examination 3			Examination 4		
	RAST (%)	RAST class	PRIST	RAST (%)	RAST class	PRIST	RAST (%)	RAST class	PRIST
Cimetidine treatment									
1	25	3	160	22	3	140	22	3	130
3	26	3	190	21	3	210	26	3	240
4	4	1	25	4	2	25	4	2	35
5	1	0	100	1	0	70	1	0	60
8	11	2	110	11	3	130	15	3	110
9	9	2	410	12	3	430	13	2	400
11	38	4	250	36	4	250	40	4	200
12	8	2	320	9	2	350	14	2	470
15	11	2	160	22	3	140	22	3	140
16	7	2	12	13	3	17	13	3	16
17	11	2	320	9	2	530	9	2	300
19	31	4	170	31	4	190	32	4	200
21	10	2	40	9	2	35	10	2	40
Mean	14.8	2.2	174	15.4	2.6	194	17	2.5	180
Placebo treatment									
2	27	3	120	28	3	130	30	3	160
6	6	2	690	6	2	940	6	2	1800
7	32	4	630	30	4	780	41	4	750
10	33	4	240	33	4	260	35	4	240
14	36	4	380	32	4	290	—	—	—
18	31	4	240	30	4	190	31	4	250
20	5	2	60	15	3	100	13	3	85
Mean	24.3	3.3	337	24.9	3.4	384	26	3.3	547

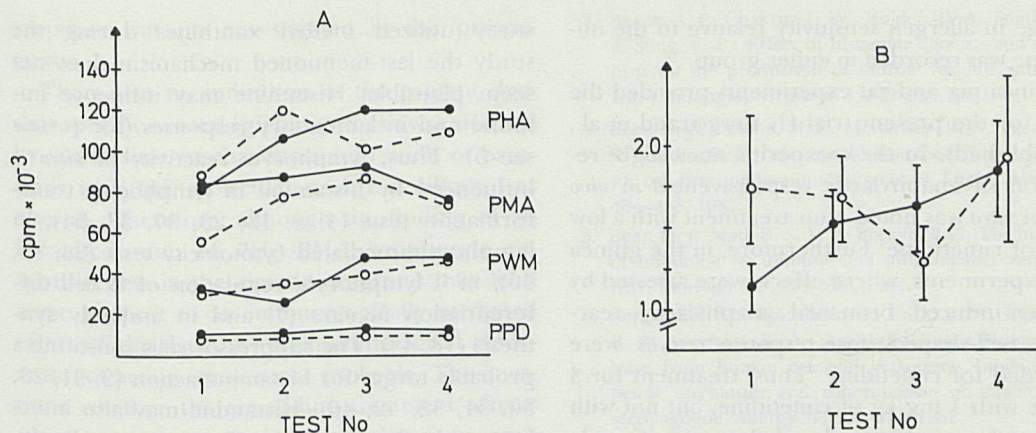


Fig. 6. A: Lymphocyte mitogen-induced ^3H -thymidine incorporation in cells from cimetidine-treated (●) and placebo-treated (○) patients. Concentrations of mitogens: PHA 1 $\mu\text{g}/\text{ml}$, PMA 0.5 $\mu\text{g}/\text{ml}$, PWM 10 $\mu\text{g}/\text{ml}$, and PPD 2.5 $\mu\text{g}/\text{ml}$. B: Ratio of PHA/PMA responsiveness of peripheral blood lymphocytes from cimetidine-treated (●) and placebo-treated (○) patients. Thymidine uptake in the cells was recorded after 3 days of incubation with either PHA (1 $\mu\text{g}/\text{ml}$) or PMA (0.5 $\mu\text{g}/\text{ml}$). The difference in PHA/PMA responsiveness between examinations 1 and 4 in the cimetidine-treated group is statistically significant ($P < 0.05$, Student's *t*-test).

duced release did not change during the treatment, whereas the allergen-induced release seemed to decrease continuously with treatment. For each secretagogue, the change in release on examinations 2, 3, and 4 in relation to that on examination 1 was calculated as the sum of the change at each of the three concentrations employed, divided by 3. Neither with respect to anti-IgE- nor with respect to allergen-induced histamine release was there any indication that the group means for the cimetidine-treated or the placebo-treated patients differed from zero (Fig. 5). Thus, judging by the results of the methods used there is no evidence that either treatment induces changes in the mean release capacity of basophil leukocytes.

Mitogen-induced lymphocyte transformation

On each visit, blood was drawn from the patients for mitogen-induced lymphocyte transformation tests. Fig. 6A shows that with none of the four mitogens studied was there any clear difference in effect between the placebo and the cimetidine group. Similarly, ConA-

induced thymidine incorporation did not differ between the groups (data not shown). The lymphocyte responsiveness to ConA, PMA, PWM and PPD did not change significantly during or after treatment in either group. However, in the cimetidine group there was a tendency towards an increased responsiveness to PHA which was not seen in the placebo-treated patients. When, for each individual and test, the PHA/PMA ratio was calculated – this ratio has previously been shown to be abnormally low in atopic subjects (39) – an increase in the ratio with time was recorded in the cimetidine but not in the placebo group (Fig. 6).

DISCUSSION

The results of the present report indicate that during treatment with a low dose of cimetidine, asymptomatic atopic asthmatic patients show significantly reduced allergen sensitivity, as revealed by bronchial challenge tests. In contrast, patients similarly treated with placebo tend to show increased allergen sensitivity. One month after the cessation of treatment, no significant

change in allergen sensitivity relative to the initial one was recorded in either group.

Guinea pig and rat experiments provided the basis for the present trial (1, Bergstrand et al., unpublished). In these experiments a slight reduction of anaphylactic responsiveness *in vivo* and *in vitro* was noted after treatment with a low dose of cimetidine. Furthermore, in the guinea pig experiments, where effects were assessed by antigen-induced bronchial anaphylactic reactions, bell-shaped dose-response curves were recorded for cimetidine. Thus, treatment for 3 weeks with 1 mg/kg of cimetidine, but not with 0.1 mg/kg or 10 mg/kg, led to significantly reduced responses in experiments performed 1 week after the cessation of treatment. Therefore, it is noteworthy that a significant effect of cimetidine was observed in the present study with the more or less arbitrarily chosen daily dose of 100 mg – which on a per weight basis would be similar to the effective dose in guinea pigs.

The change in allergen sensitivity induced by cimetidine treatment may be considered small. Thus, 14 days after the initiation of treatment, cimetidine-treated patients tolerate approximately twice as much allergen as do placebo-treated patients. It is difficult to estimate the clinical relevance which such a reduction in allergen sensitivity may have. It has been reported that immunotherapy with cat pelt extract results in an approximately ten-fold decrease in bronchial sensitivity to the allergen. Again, the relation between the observed decrease in bronchial sensitivity to allergen and the patient's tolerance to cats is not known (45).

The reason for the observed effect of cimetidine has not been determined. We (19) and others (16) have previously failed to find any effect of single doses of cimetidine on allergen-induced bronchoconstriction. We therefore do not consider the direct interference of cimetidine with H_2 -receptors on airway smooth muscle or mast cells to be a likely explanation of the effect. A number of other explanations may tentatively be advanced. These include non-immunological mechanisms of action – e.g. the induction of catecholamine release (24) or a decrease in methyl xanthine metabolism (14, 52). Since none of the patients in the present

study utilized methyl xanthines during the study the last-mentioned mechanism does not seem plausible. Histamine may influence immune and inflammatory responses (for review see 5). Thus, lymphocyte reactivity *in vitro* is influenced by histamine in lymphocyte transformation tests (4, 8, 13, 23, 37, 38, 51), in lymphocyte-mediated cytotoxicity tests (28, 35, 36), in T-lymphocyte regulation of B cell differentiation *in vitro* (7) and in antibody synthesis (18, 43). The suppressor cells constitute a probable target for histamine action (2, 21, 23, 30, 31, 33, 42, 46). Histamine may also interfere with the synthesis of reaginic antibody, through the activation of suppressor cells. Baker et al. (3) reported that treatment with histamine H_2 -agonists inhibited and with H_2 -antagonists enhanced the primary but not the secondary murine reaginic antibody response. Rocklin et al. (32) recorded the generation of allergen-specific suppressor cells expressing H_2 -receptors during immunotherapy. Although interference with H_2 -receptors was demonstrated in some of these studies, structure-activity studies in several systems failed to define unequivocally the type of receptors involved (8, 35, 36, 50).

Lymphoid cells from atopic individuals may react abnormally to histamine. Thus, Strannegård & Strannegård (37) and Brostoff and co-workers (for ref. see 12) showed that lymphocytes from atopic individuals are more sensitive than cells from normal individuals to histamine-mediated inhibition of mitogen-induced thymidine incorporation. Furthermore, Beer et al. (4) reported that atopic patients showed abnormal histamine-induced suppressor cell function.

Therefore potential mechanisms of action of cimetidine on the immunological level include interference with the synthesis of IgE antibody or with the process of their binding to the target tissue. It is also possible that the drug interferes with the response of the target organ to released mediators – e.g., in some way reduces the non-specific bronchial hyperreactivity connected with the asthmatic state. Cimetidine treatment may block the increase in non-specific hyperreactivity which is recorded after allergen challenge inducing a late response (9). The late

response was not investigated in the present study.

There was no indication in the present data that specific or total IgE biosynthesis was affected by cimetidine, or that the sensitization of basophils with IgE molecules or IgE antibody was altered. Therefore, although the finding of an increased ratio of PHA/PMA lymphocyte responsiveness in the cimetidine group may lend some support to an immunologically mediated effect of the drug, a non-immunological mechanism of action seems more probable. The questions whether the cimetidine treatment affects target organ sensitivity or influences non-specific bronchial hyperreactivity cannot be answered by the present results.

In conclusion, it may be said that the treatment of allergic but asymptomatic asthmatic patients with a low dose of cimetidine induces a slight but significantly decreased allergen sensitivity, as revealed by bronchial allergen challenge. The reason for this effect is not clear but an interference by the drug with either the process of sensitization of the target tissue or the state of non-specific bronchial hyperreactivity may be suspected.

ACKNOWLEDGEMENTS

Dr. C. J. Lamm kindly performed the statistical evaluation of the data. The skilful technical assistance of B. Balder, A. Björnsson, I.-M. Frick, P. Lehtonen, L. Lopenen, and B. Lundquist is gratefully acknowledged. Mrs. U. Larsson kindly typed the manuscript.

This study was supported in part by a grant from the Swedish Medical Research Foundation (project No. 3942).

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