

Comparison of the effects on bronchial hyperresponsiveness of antiallergic agents and beclomethasone dipropionate in long-term bronchial asthma

A retrospective study

Hoshino K, Kawasaki A, Mizushima Y, Oosaki R, Yano S, Kobayashi M. Comparison of the effects on bronchial hyperresponsiveness of antiallergic agents and beclomethasone dipropionate in long-term bronchial asthma. Allergy 1993; 48: 196–201. © Munksgaard 1993.

The effect of antiallergic agents (DSCG (disodium cromoglycate), ketotifen, and ibudilast) and beclomethasone dipropionate inhaler (BDI) on bronchial hyperresponsiveness to histamine inhalation was retrospectively assessed in 72 asthmatic patients with more than a year's duration of the disease. Decrease in bronchial hyperresponsiveness to histamine was observed in 10 out of the 33 (30%) antiallergic-agents-treated patients (group A, mean duration = 7.8 months), in 12 of 19 (63.2%) BDI-treated patients (group B, 6.2 months), but only 2 of the 20 (10%) control patients (group C, 7.8 months). Improvement of histamine PC₂₀ was from 310 to 597 µg/ml ($P < 0.01$) in group A, from 308 to 1622 µg/ml ($P < 0.0005$) in group B, and from 575 to 525 µg/ml (NS) in group C. A significant decrease in the peripheral eosinophil count was observed only in group B. The improvement in bronchial hyperresponsiveness was parallel with that of asthmatic symptoms; the percentage of patients becoming symptom-free rose from 12 to 42%, 5 to 89%, and 5 to 20% in groups A, B, and C, respectively. Out of 11 unimproved patients in group A, 7 showed a significant improvement in their histamine PC₂₀ by BDI treatment (mean PC₂₀: 311 → 1828 µg/ml). These results suggest that BDI might be more effective than antiallergic agents in the treatment of patients with long-standing bronchial asthma.

K. Hoshino, A. Kawasaki, Y. Mizushima, R. Oosaki, S. Yano, M. Kobayashi

First Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan

Key words: antiallergic agents; beclomethasone dipropionate; bronchial asthma; bronchial hyperresponsiveness.

Yutaka Mizushima, MD
First Department of Internal Medicine
Toyama Medical and Pharmaceutical University
Sugitani 2630, Toyama 930-01
Japan

Accepted for publication 16 September 1992

Bronchial hyperresponsiveness to specific or non-specific stimuli has been well documented as characteristic of bronchial asthma (2, 9, 18). In Japan, various oral antiallergic agents have recently been developed and used for the treatment of bronchial asthma (6, 12, 14–17, 20–22). At present, 11 antiallergic agents are commercially available. The antiallergic agents are classified into three groups according to their chemical structure and pharmacologic action. Group I is an acidic type which includes DSCG (disodium cromoglycate), tranilast, amlexanox, repirinast, tazanolast, and pemirolast (20, 21). These agents inhibit mainly the release of histamine from mast cells. Group II is a basic type which includes ketotifen, azelastine, terfenadine, and oxatomide (6, 16). These agents inhibit the release of chemical mediators (LTs, PAF, etc.) from eosino-

phils and neutrophils as well as from mast cells. The agents in this group have an antihistamine effect. Group III is a purazolopyridine derivative which includes ibudilast (14). This agent does not inhibit the release of histamine, but does enhance the PGI₂ effects (17).

We have previously reported (12) that antiallergic agents might be used to treat asthmatic patients, especially in disease with a duration of less than 1 year. We have further examined the effect of antiallergic agents on nonspecific bronchial hyperresponsiveness in patients with long-standing asthma (more than 1 year's duration). In the present study, we assessed retrospectively their effect on bronchial hyperresponsiveness in comparison with that of beclomethasone dipropionate inhaler (BDI).

Subject and methods

Subject and study design

The effect of antiallergic agents, BDP, or only bronchodilators on bronchial hyperresponsiveness was retrospectively assessed in 72 patients diagnosed as having bronchial asthma (1). The subjects were used in this study in 1987–91. Their asthmatic symptoms had occurred for more than 1 year before the study, and they were all nonsmokers. Patients who received oral corticosteroid or gold therapy were excluded. All patients were initially treated with beta-stimulants and/or xanthine-derivatives. When asthmatic symptoms were well controlled, antiallergic agents (group A; 33 cases; DSCG 10, ketotifen 6, ibudilast 17) or BDP (group B; 19 cases) was randomly administered in addition to beta-stimulants and/or xanthines. As a control group, they were given only beta-stimulants and/or xanthine (group C; 20 cases). The bronchial hyperresponsiveness was examined in patients who had antiallergic agents or BDP for at least 3 months, and the evaluation was made retrospectively. An increase of the histamine threshold (PC_{20}) after the treatment of more than fourfold was defined as improvement in bronchial hyperresponsiveness. Severity of asthmatic symptoms was evaluated in the month before each histamine inhalation test. Symptoms were classified into four grades; severe, moderate, mild, and symptom-free in accordance with the strength and the frequency of asthmatic attacks in the 1-month period before each test. In brief, "severe" meant moderate attacks more than 4 d/week; "moderate", mild attacks more than 4 d/week; and "mild", only a wheeze more than 4 d/week.

Agents

Antiallergic agents used in this study included DSCG (Fujisawa Pharmaceutical Co., Ltd) (administered by "spinhaler", 20 mg $\times$ 4/d), ibudilast (14, 17) (Kyorin Pharmaceutical Co., Ltd), and ketotifen (16) (Sandoz Pharmaceutical Co., Ltd) (the last two administered orally 10 mg $\times$ 2/d, 1 mg $\times$ 2/d). BDP (Glaxo Co., Ltd) was administered by meter-dosed inhaler (50 μ g) four times a day, 1–4 puffs each time (mean 7 puffs/d).

Histamine inhalation test

The histamine inhalation test was conducted by the method stipulated by the Japanese Society of Allergology. Briefly, aerosols were generated with a DeVilbiss nebulizer (type 646) at an airflow of 5 l/min. Inhalation occurred for 2 min during quiet breathing through the mouth at 5-min intervals. An isotonic 0.9% saline solution was inhaled first, followed by

escalating concentrations of histamine from 20 to 10 000 μ g/ml in twofold increments. The FEV_1 was measured before saline solution inhalation and after each histamine inhalation. The test was continued until the FEV_1 had fallen by 20% or until the highest concentration of histamine (10 000 μ g/ml) had been administered. The threshold was defined as the lowest concentration of histamine which resulted in a 20% fall of FEV_1 . Histamine PC_{20} was calculated by linear interpolation between the last two data points on the dose-response curve, or was expressed as "> 10 000 μ g/ml" if there had been no response. The mean value of PC_{20} was expressed as a geometric one or as the mean of converted concentration of histamine (μ g/ml). Before the histamine inhalation test, the basic type of antiallergic agents which have antihistamine activities were withheld for 4 d and other drugs for 24 h. In order to avoid possible daily changes in response to histamine, we performed the test between 0900 and 1200 in the morning.

Statistical analysis

Data were expressed as the mean $\pm$ SD, and statistical significance, evaluated by Student's *t*-test, Wilcoxon's *t*-test, or the Mann-Whitney U-test, was set at $P < 0.05$.

Results

Decrease in bronchial hyperresponsiveness to histamine inhalation by treatment with antiallergic agents or BDP

Changes in bronchial hyperresponsiveness to histamine inhalation were compared among subjects treated by antiallergic agents (group A), by BDP (group B), and by only beta-stimulants and/or xan-

Table 1. Patients' characteristics in three groups

	Antiallergic agents (A) group	Beclomethasone (B) group	Control (C) group
Number of patients	33	19	20
Gender, M/F	20/13	12/7	13/7
Age (yr)	39.2 (15–79)	42.3 (19–70)	45.2 (17–72)
Extrinsic/intrinsic	18/15	8/11	10/10
Duration of disease (yr)	11.0 (1–43)	7.8 (1–30)	10.7 (1–41)
FEV_1 (l)	2.38 $\pm$ 0.88	2.27 $\pm$ 0.59	2.17 $\pm$ 0.89
% FEV_1 (%)	77.4 $\pm$ 14.8	77.3 $\pm$ 19.4	73.2 $\pm$ 20.8
PC_{20} (μ g/ml)	309.0	307.8	575.4
Log (PC_{20})	(2.49 $\pm$ 0.59)	(2.49 $\pm$ 0.60)	(2.76 $\pm$ 0.62)
Serum IgE (U/ml)	455 $\pm$ 569	271 $\pm$ 278	327 $\pm$ 402
Peripheral blood eosinophil counts (/ μ l)	397 $\pm$ 283	415 $\pm$ 237	415 $\pm$ 233
Administration periods (mo)	7.8 $\pm$ 5.9	6.2 $\pm$ 3.8	7.8 $\pm$ 6.1

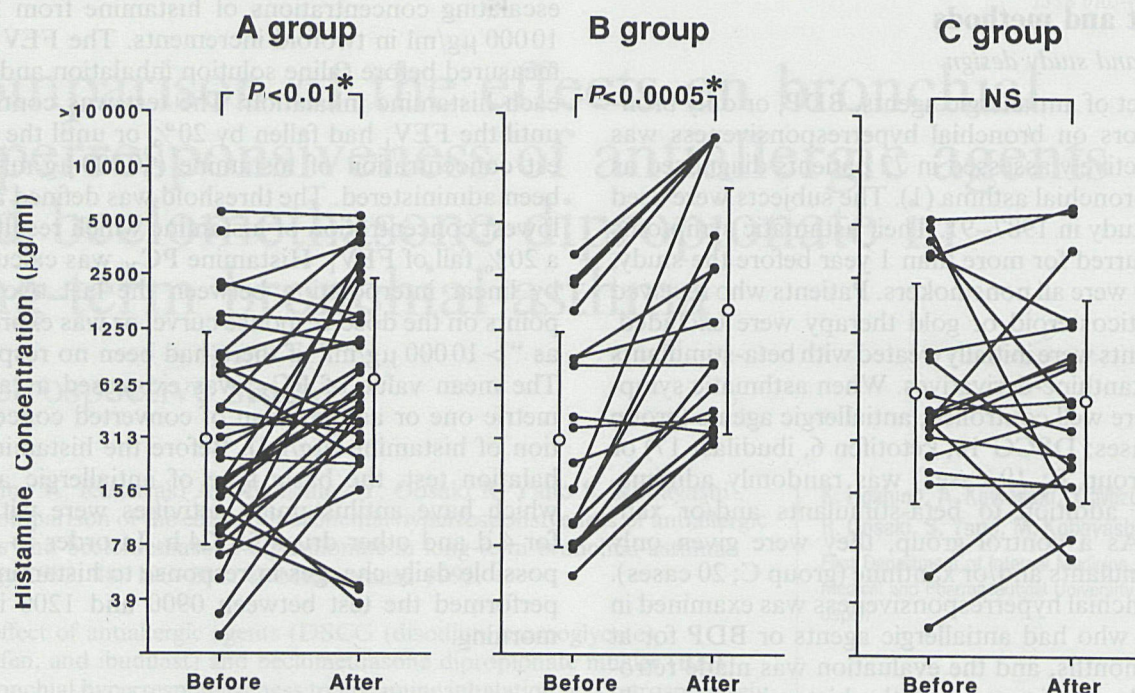


Fig. 1. Changes in histamine threshold (PC_{20}) in three groups. * Statistical analysis by Wilcoxon's test.

thines (group C). There was no significant difference in clinical characteristics among the three groups (Table 1). A decrease in bronchial hyperresponsiveness to histamine inhalation was observed in 10 out of the 33 patients who were treated with antiallergic agents, in 12 out of the 19 who were treated with BDP, and in 2 out of the 20 who were treated with only beta-stimulants and/or xanthines (Fig. 1). Improvement of histamine PC_{20} (geometric mean $\pm$ SD) was from 309 to 597 $\mu\text{g/ml}$ ($2.49 \pm 0.59 \rightarrow 2.81 \pm 0.57$; $P < 0.01$) in group A, 308 to 1622 $\mu\text{g/ml}$ ($2.49 \pm 0.60 \rightarrow 3.21 \pm 0.68$; $P < 0.0005$) in group B, and 575 to 525 $\mu\text{g/ml}$ ($2.75 \pm 0.62 \rightarrow 2.72 \pm 0.57$, NS) in group C. Difference in $\log(PC_{20})$ before and after the treatment was 0.30 ± 0.54 in group A, 0.72 ± 0.54 in group B, and -0.038 ± 0.58 in group C. There were statistical differences in improvement of $\log(PC_{20})$ between groups A and B ($P < 0.005$) and groups B and C ($P < 0.0005$) by the Mann-Whitney U-test. Patients whose histamine threshold reached more than 10000 $\mu\text{g/ml}$ after treatment were observed only in group B (5/19). No significant difference could be observed in improvement of PC_{20} among DSCG, ketotifen, and ibudilast groups; difference in $\log(PC_{20})$ was 0.49 ± 0.66 in the DSCG group ($n = 10$), 0.16 ± 0.46 in the ibudilast group ($n = 17$), and 0.48 ± 0.57 in the ketotifen group ($n = 6$) (Fig. 2).

There was no significant change in FEV_1 , % FEV_1 , and serum IgE in the three groups. However, a decrease in peripheral eosinophil count was observed only in group B (415 to 320/ μl ; $P < 0.05$) (Table 2).

Table 2. Changes in parameters in three groups

Group		FEV_1 (l)	% FEV_1 * (%)	Serum IgE (U/ml)	Peripheral blood eosinophil counts (/ μl)
A group	Before	2.38 ± 0.88	77.4 ± 14.8	455 ± 568	396 ± 287
	After	2.37 ± 0.59	75.9 ± 13.1	494 ± 625	341 ± 217
B group	Before	2.27 ± 0.59	77.3 ± 19.4	271 ± 278	415 ± 237
	After	2.45 ± 0.47	82.1 ± 13.5	275 ± 285	$320 \pm 161^{**}$
C group	Before	2.17 ± 0.89	7.32 ± 20.8	326 ± 402	414 ± 233
	After	2.14 ± 1.00	71.9 ± 22.6	243 ± 272	412 ± 233

* Normal values for FEV_1 were calculated by Berglund's formula.

** $P < 0.05$ by Student's *t*-test.

Changes in severity of asthmatic symptoms in the three groups

Changes in severity of asthmatic symptoms were compared among the three groups. As shown in Fig. 3, the percentage of patients who became symptom-free increased from 12 to 42% in group A, 5 to 89% in group B, and 5 to 20% in group C. The most remarkable improvement in asthmatic symptoms was observed in the BDI-treated group.

Effect of BDP on bronchial hyperresponsiveness in unimproved patients treated with antiallergic agents

Among the 23 patients in group A whose bronchial hyperresponsiveness had not significantly improved with antiallergic agents treatment, 11 patients were

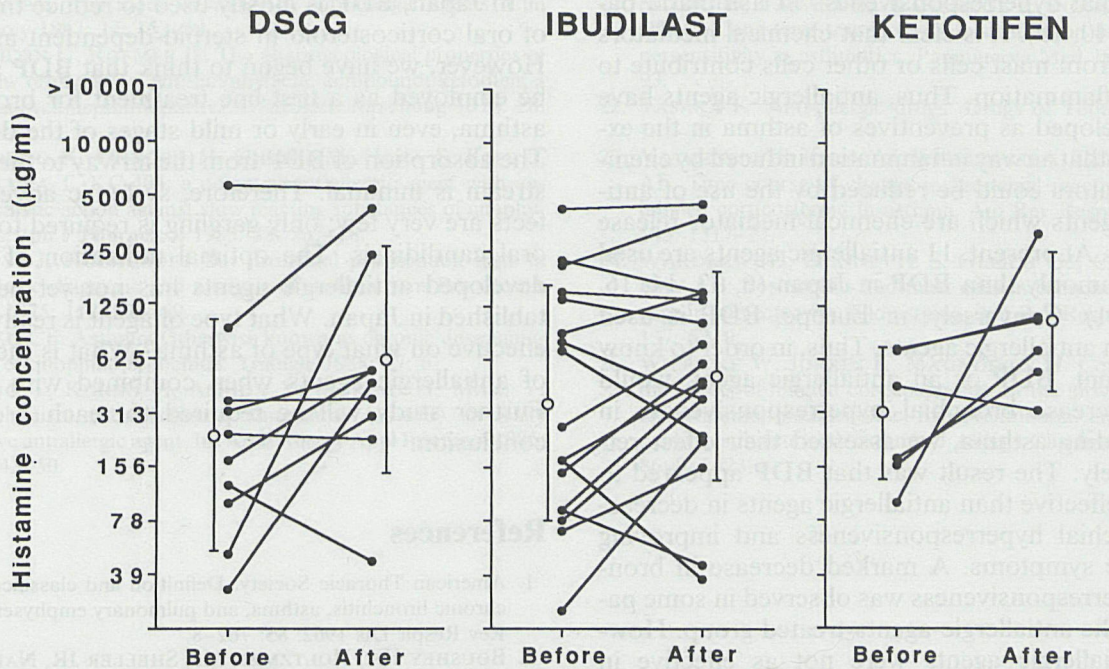


Fig. 2. Changes in histamine threshold (PC_{20}) in three antiallergic agent groups.

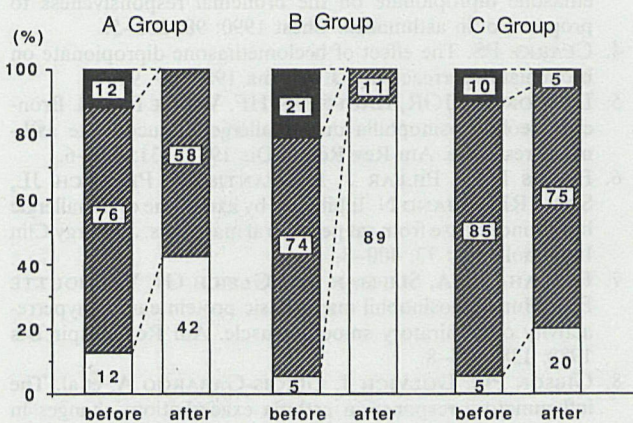


Fig. 3. Changes in asthmatic symptoms in three groups. Dark area, moderate; hatched area, mild; unshaded area, symptom-free.

followed by BDI treatment. The remaining 12 patients did not accept the BDI treatment. Administration periods were almost equal between the two agents (10 months each). As shown in Fig. 4, a decrease in bronchial hyperresponsiveness in a period of treatment with BDI was observed in 7 out of 11 patients (PC_{20} ; $311 \rightarrow 1828 \mu\text{g/ml}$; $P < 0.05$ by Wilcoxon's test). There was a significant difference in improvement between antiallergic agents and BDP groups by the Mann-Whitney U-test ($P < 0.05$).

Discussion

Airway inflammation has recently received much attention as an important source of the pathogenesis

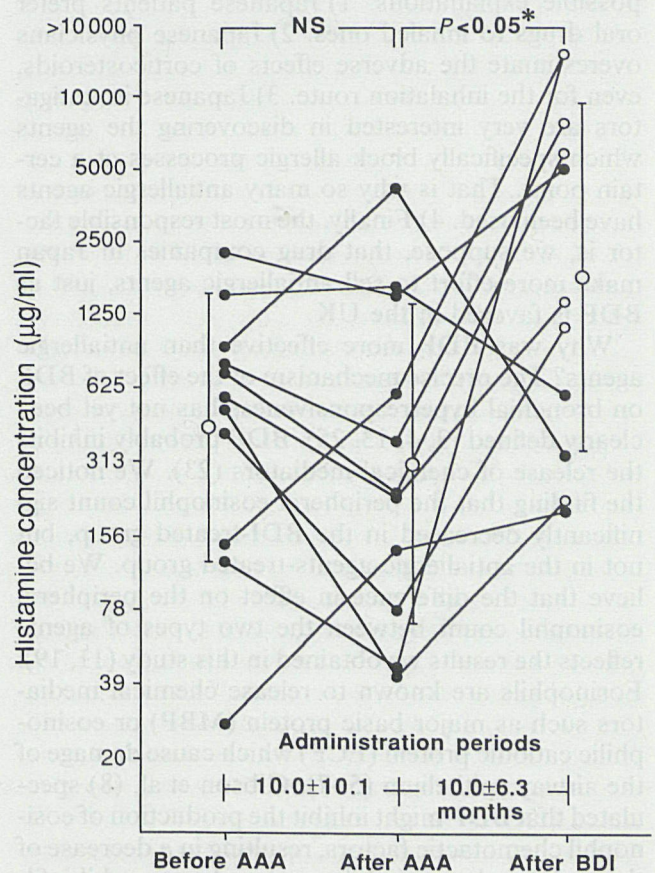


Fig. 4. Effect of BDI on histamine threshold (PC_{20}) in unimproved patients who had been treated with antiallergic agents (AAA). * Statistical analysis by Wilcoxon's test.

of bronchial hyperresponsiveness in asthmatic patients (8, 10, 19). It is clear that chemical mediators released from mast cells or other cells contribute to airway inflammation. Thus, antiallergic agents have been developed as preventives of asthma in the expectation that airway inflammation induced by chemical mediators could be reduced by the use of anti-allergic agents which are chemical-mediator-release inhibitors. At present, 11 antiallergic agents are used more commonly than BDP in Japan (6, 12, 14, 16, 17, 20, 21). Conversely, in Europe, BDP is used more than antiallergic agents. Thus, in order to know which agent, BDP or an antiallergic agent, would better decrease bronchial hyperresponsiveness in long-standing asthma, we assessed their effect retrospectively. The result was that BDP appeared to be more effective than antiallergic agents in decreasing bronchial hyperresponsiveness and improving asthmatic symptoms. A marked decrease in bronchial hyperresponsiveness was observed in some patients in the antiallergic-agents-treated group. However, antiallergic agents were not as effective in patients with long-standing asthma as in patients with short-term asthma (12).

Why have antiallergic agents been favored over inhaled corticosteroids in Japan? There are several possible explanations: 1) Japanese patients prefer oral drugs to inhaled ones. 2) Japanese physicians overestimate the adverse effects of corticosteroids, even for the inhalation route. 3) Japanese investigators are very interested in discovering the agents which specifically block allergic processes at a certain point. That is why so many antiallergic agents have been used. 4) Finally, the most responsible factor is, we suppose, that drug companies in Japan make more effort to sell antiallergic agents, just as BDP is favored in the UK.

Why was BDP more effective than antiallergic agents? The precise mechanism of the effect of BDP on bronchial hyperresponsiveness has not yet been clearly defined (3, 4, 13, 25). BDP probably inhibits the release of chemical mediators (23). We noticed the finding that the peripheral eosinophil count significantly decreased in the BDI-treated group, but not in the antiallergic-agents-treated group. We believe that the difference in effect on the peripheral eosinophil count between the two types of agents reflects the results we obtained in this study (11, 19). Eosinophils are known to release chemical mediators such as major basic protein (MBP) or eosinophilic cationic protein (ECP) which cause damage of the airway epithelium (5–7). Gibson et al. (8) speculated that BDP might inhibit the production of eosinophil chemotactic factors, resulting in a decrease of the peripheral eosinophil count and eosinophil infiltration into the airway epithelium. We have reached a similar conclusion.

In Japan, BDP is mostly used to reduce the dose of oral corticosteroid in steroid-dependent asthma. However, we have begun to think that BDP should be employed as a first-line treatment for bronchial asthma, even in early or mild stages of the disease. The absorption of BDP from the airway to the blood stream is minimal. Therefore, systemic adverse effects are very few; only gargling is required to avoid oral candidiasis. The optimal utilization of newly developed antiallergic agents has not yet been established in Japan. What type of agent is really more effective on what type of asthma? What is the effect of antiallergic agents when combined with BDP? Further study will be required to reach a certain conclusion.

References

1. American Thoracic Society. Definition and classification of chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1962; 85: 762–8.
2. BOUSHEY HA, HOLTZMAN MJ, SELLER JR, NADEL JA. Bronchial hyperreactivity. *Am Rev Respir Dis* 1980; 121: 389–413.
3. CARPENTIERE G, CASTELLO F, MARIO S. Effect of beclomethasone dipropionate on the bronchial responsiveness to propranolol in asthmatics. *Chest* 1990; 98: 263–5.
4. CLARKE PS. The effect of beclomethasone dipropionate on bronchial hyperreactivity. *J Asthma* 1982; 19: 91–3.
5. DE MONCHY JGR, KAUFFMAN HF, VENGE P, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic response. *Am Rev Respir Dis* 1985; 131: 373–6.
6. FIELDS DAS, PILLAR J, DIAMANTIS W, PERHACH JL, SOFIA RD, CHAND N. Inhibition by azelastine of nonallergic histamine release from rat peripheral mast cells. *J Allergy Clin Immunol* 1984; 73: 400–3.
7. FLAVAHAN NA, SLIFMAN NR, GLEICH GJ, VANHOUTTE PM. Human eosinophil major basic protein causes hyperreactivity of respiratory smooth muscle. *Am Rev Respir Dis* 1988; 138: 685–8.
8. GIBSON PG, DOLVICH J, GIRGIS-GABARGO A, et al. The inflammatory response in asthma exacerbation: changes in circulating eosinophils, basophils and their progenitors. *Clin Exp Allergy* 1990; 20: 661–8.
9. HARGREAVE FE, DOLOVICH J, O'BYRNE PM, RAMSDALE EH, DANIEL EE. The origin of airway hyperresponsiveness. *J Allergy Clin Immunol* 1986; 78: 825–32.
10. HARGREAVE FE, RAMSDALE EH, KIRBY JG, O'BYRNE PM. Asthma and the role of inflammation. *Eur J Respir Dis* 1986; 69 (Suppl. 147): 16–21.
11. HORN BR, ROBIN ED, THEODORE J, VAN KESSEL A. Total eosinophil counts in the management of bronchial asthma. *N Engl J Med* 1975; 292: 1152–5.
12. HOSHINO K, KAWASAKI A, MIZUSHIMA Y, YANO S. Effect of antiallergic agents and bronchial hypersensitivity in short-term bronchial asthma. *Chest* 1991; 100: 57–62.
13. JUNIPER EF, KLINE PA, VANZIELEGHEM MA, RAMSDALE EH, O'BYRNE PM, HARGREAVE FE. Effect of long-term treatment with inhaled corticosteroid (Budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990; 142: 832–6.
14. KAWASAKI A, HOSHINO K, OOSAKI R, MIZUSHIMA Y, YANO S. Effect of ibudilast, a novel anti-allergic agent, on airway hypersensitivity in bronchial asthma. *J Asthma* 1992; 29: 245–52.

15. KAY AB. The mode of action of anti-allergic agents. *Clin Allergy* 1987; 17: 153-64.
16. MARTIN U, ROEMER D. The pharmacological properties of a new orally active anti-anaphylactic compound: ketotifen, a benzocycloheptathiophene. *Arzneimittelforschung* 1978; 28: 770-82.
17. NISHINO K, OHKUBO H, OHASHI M, HARA S, KITO J, IRIKURA T. KC-404: a potential antiallergic agent with antagonistic action against slow reacting substances of anaphylaxis. *Jpn J Pharmacol* 1983; 33: 267-78.
18. PEPYS J, HUCHCROFT BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975; 112: 829-59.
19. READ CE. Asthma. Otherwise known as chronic desquamative eosinophilic bronchitis. *Triangle* 1988; 27: 61.
20. SAJO T, KURIKI H, ASHIDA Y, MAKINO H, MAKI Y. Mechanism of the action of amoxanox (AA-673), an orally active antiallergic agent. *Int Arch Allergy Appl Immunol* 1985; 78: 43-50.
21. SUZUKI H, TANAKA K, KANESHIGE K, NOGUCHI E. The effect of long-term tranilast administration on bronchial hypersensitivity in asthmatics. *Panminerva Med* 1989; 31: 88-93.
22. TASAKA K. Anti-allergic drugs. *Drugs of Today* 1986; 22: 101-33.
23. VATHENEN AS, KNOX AJ, WISNIEWSKI A, TATTERSFIELD AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991; 143: 1317-21.
24. WARDLAW AJ, DUNNETTE S, GLEICH GJ, COLLINS JV, KAY AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma. *Am Rev Respir Dis* 1988; 137: 62-9.
25. WIEBICKE W, JORRES R, MAGNUSSEN H. Comparison of the effects of inhaled corticosteroids on the airway response to histamine, methacholine, hyperventilation, and sulfur dioxide in subjects with asthma. *J Allergy Clin Immunol* 1990; 86: 915-23.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.