

Long-Term Modification on Histamine-Induced Bronchoconstriction by Disodium Cromoglycate and Ketotifen versus Placebo

F. GOZALO REQUES, C. COLAS SANZ, C. SENENT SANCHEZ, M. RUBIO SOTES, T. HERRERO LOPEZ and M. DE BARRIO FERNANDEZ

Allergy Section (2nd Dept. of Internal Medicine) Hospital Provincial de Madrid, Madrid, Spain

In order to compare long-term changes induced on a wide spectrum of bronchial hyperactivity (BH) by the antiallergic drugs disodium cromoglycate (DSCG) and ketotifen, 56 asthmatic patients (age range 15-55 years) were studied. Patients were allocated to three groups with similar age and BH level. During 2 months, 15 individuals inhaled 20 mg DSCG four times a day, 14 took ketotifen 1 mg twice a day orally and 14 one placebo (lactose) capsule twice a day. After preliminary results, an additional group of 13 patients took clemastine 1 mg orally twice a day for 1 week. Only the ketotifen and clemastine groups differed significantly from the placebo group on shifting log dose-response curves of inhaled histamine. In addition, no significant difference was seen between the ketotifen and clemastine groups. These results suggest that changes induced by ketotifen were mainly related to its powerful antihistamine action; similarly, nonspecific BH is not wholly dependent on mediator release.

Key words: asthma; bronchial hyperactivity; disodium cromoglycate; ketotifen.

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The allergic mediators released from sensitized mast cells in the lumen of airways, open the tight interepithelial junctions and allow the access of allergens and other mediators released either to the irritant receptors or to the deeper mast cells in the submucosa (21, 22, 39). In this way Patterson (33) was able to transfer transient bronchial hyperactivity (BH) to inhaled allergens from the intraluminal mast cells of sensitized primates to non-sensitized individuals.

Mast cell degranulation is related to the production of superoxide anion and other toxic radicals that could damage cellular membranes and cause epithelial desquamation (7). On the other hand, attracted eosinophils, through their major basic protein, also cause epithelial stripping and encourage ulterior degranulation of mast cells by their peroxidase enzyme (17).

The dose-response curve of inhaled histamine has been shown as a useful tool for determining the degree of nonspecific BH in extrinsic or intrinsic asthmatics (9). This test is highly reproducible and easy to correlate with other bronchoconstrictor agents (8, 24).

The ability of disodium cromoglycate (DSCG) to inhibit mediator release from mast cells is well documented (11, 23). In recent years new antiallergic drugs of oral efficacy have been tested, but only in animal models. One of these, the benzocycloheptathiophene, ketotifen (HC 20-511), besides having a powerful antihistamine effect, has an antiallergic action *in vitro* (19, 28, 40), and offers a moderately effective suppression of early response to allergenic bronchial challenges to acetylsalicylic acid (ASA) or exercise (12, 42).

The aim of this clinical assay was to deter-

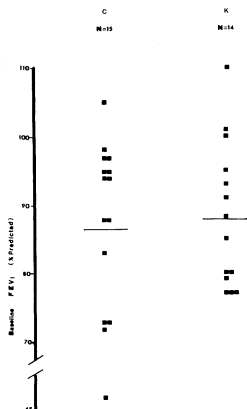


Fig. 1. Individual values of FEV_1 (% predicted) in disodium cromoglycate (C) and ketotifen (K) groups. Horizontal lines: mean values. Note the similarity of both samples in degree of airways obstruction.

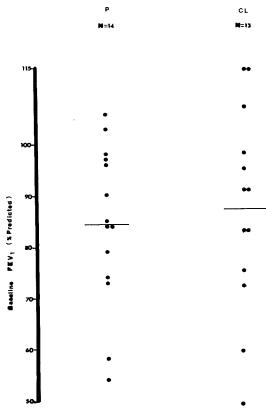


Fig. 2. Individual values of FEV_1 (% predicted) in placebo (P) and clemastine (Cl) groups. Horizontal lines: mean values. As in Fig. 1 these additional samples show a similar wide range of airways obstruction.

mine, using a wide range of values, the long-term ability of DSCG and ketotifen to improve nonspecific BH in asthmatics in comparison with clemastine fumarate, dimethylchlor-diphenyl-pyrrolidine (a conventional H_1 antagonist), using habitual dosages and methods of administration.

MATERIAL AND METHODS

Fifty-six outpatients (17 men and 39 women; age 35.2 ± 13.3 years) with extrinsic (seasonal or perennial) and intrinsic asthma were studied. The diagnosis was based on clinical history, skin

test to environmental aeroallergens and occasionally by determination of serum specific IgE (RAST procedure). Patients with forced expiratory volume in 1 sec (FEV_1) below 1.5 were excluded (Figs. 1, 2).

The patients were allotted to three initial treatment groups:

C Group (DSCG). 15 patients (9 females and 6 males) 10 with extrinsic and five with intrinsic asthma. Age: 33.4 ± 12.7 years. They all inhaled 20 mg DSCG, using a Spinhaler device, four times a day for 8 weeks.

K Group (Ketotifen). 14 patients (11 females and 3 males) eight with extrinsic and six with intrinsic asthma. Age: 35.6 ± 13.4 years. They

were treated with 1 mg ketotifen orally, twice daily for 8 weeks.

P Group (Placebo). 14 patients (12 females and 2 males) 10 with extrinsic and four with intrinsic asthma. Age: 36.8 ± 11.7 years. They took one capsule of lactose twice daily for 8 weeks.

After preliminary results, an additional group CI Group (Clemastine), was formed. 13 patients (7 females and 6 males) eight allergics and five nonallergics. Age: 35.2 ± 16.5 years. They took 1 mg clemastine, orally, twice daily for 1 week.

Groups C, K and P were retested at 8 weeks and Group CI at 1 week. Patients with asthma attacks and/or upper respiratory infections before testing were excluded. Seasonal asthmatics were studied out of season. Maximal variation of baseline FEV₁ values were $\leq 18\%$, between first and second challenges (Tables 1, 2). Those patients on a DSCG or ketotifen regimen prior to testing, attended a wash-out period of 2 weeks before entering the study.

Antiasthmatic concomitant treatment is shown in Tables 1 and 2. In the case of exacerbation during the trial, patients had the possibility of contacting us. The clinical treatment criteria were the following:

- Patients on no additional drug therapy used salbutamol aerosol for 5 days.
- Patients using bronchodilators or beclomethasone "around the clock" were given a single morning dose of 0.5–0 mg/kg/day M-prednisolone for 5 days.
- Patients on systemic corticosteroids received boost therapy to the maintenance dose.
- In the case of purulent sputum, amoxicillin, 2 g/day was given for 8 days.

Drug withdrawals before initial and final histamine challenge were, according to American Thoracic Society standards (13), the following: β -adrenergic bronchodilators: 8 h before; theophylline or derivatives: 24 h before; antihistamines: 48 h before (hydroxyzine: 72 h before). Corticosteroids (systemic or inhaled) were allowed at the given dose throughout the study.

Self-administration was periodically assessed by phone. All patients gave informed consent and the study protocol was approved by the

Clinical Trial Committee of the Provincial Hospital of Madrid.

Table 1

Clinical data from disodium cromoglycate and ketotifen groups

Patient No.	Sex	Age (years)	Cromolyn group		Asthma type	Concomitant treatment
			Baseline FEV ₁ variation 1st–2nd test (%)			
1	M	29	5	A.P.	I	
2	F	19	2	A.S.	I	
3	M	17	5	A.P.	—	
4	M	14	5	A.P.	I	
5	M	25	2	O	T	
6	F	20	15	A.P.	T	
7	F	28	10	NA-AI	B + β_2	
8	M	38	0	A.P.	B + β_2 + I	
9	F	44	13	A.P.	B + I	
10	F	36	12	A.P.	—	
11	F	48	11	NA-AI	T + B + β_2	
12	M	38	8	A.P.	β_2	
13	F	54	11	NA-AI	C + β_2	
14	F	49	4	NA-AI	T	
15	F	42	4	N.A.	B	

Patient No.	Sex	Age (years)	Ketotifen group		Asthma type	Concomitant treatment
			Baseline FEV ₁ variation 1st–2nd test (%)			
1	F	16	2	A.P.	β_2	
2	M	16	9	A.P.	I	
3	F	29	18	A.P.	B + β_2	
4	M	19	4	A.S.	—	
5	F	32	4	N.A.	B + β_2 + T	
6	F	22	15	N.A.	β_2 + T	
7	F	43	1	N.A.	B + β_2 + T	
8	F	50	10	N.A.	B + T	
9	M	55	3	N.A.	B + β_2	
10	F	45	17	N.A.	β_2 + T	
11	F	42	1	A.P.	β_2 + T + I	
12	F	48	10	A.P.	B + T	
13	F	37	0	A.P.	β_2 + I	
14	F	42	4	A.P.	I	

AP: allergic perennial, AS: allergic seasonal; O: occupational, NA: nonallergic; AI: aspirin idiosyncrasy, I: immunotherapy, T: theophylline, B: beclomethasone dipropionate, β_2 : beta 2-adrenergic drugs, C: corticosteroids.

Histamine challenge test

The method employed has been described by Cockcroft et al. (9). Pulmonary function was assessed with a dry spirometer (Volumograph

DS Mijhardt). Nebulizers with a flow of 7 l/min (Hudson® Mod. 1720) were used. The output ranges between 0.14–0.16 ml/min (37) and the average size of particles delivered was $1.6 \pm 0.5 \mu$. Histamine HCl was diluted with phosphate buffered saline at pH 7.2.

After determination of baseline FEV₁ (best of three) the patient inhales the saline solution, for 2 min at tidal volume, through a mouth-piece connected to the nebulizer and with nose occluded. After 30 and 90 sec the FEV₁ is measured again. The patient then inhales two-fold histamine solutions (0.03–32 mg/ml). The FEV₁ is determined 30, 90 sec, and 5 min after each solution until a fall of at least 20% of the lowest post saline value is reached.

Table 2

Clinical data from clemastine and placebo groups. For abbreviations see Table 1. Note similarities between age and asthma type of both patient samples and the low number of subjects requiring corticosteroids

Clemastine group					
Patient No.	Sex	Age (years)	Baseline FEV ₁ variation 1st–2nd test (%)	Asthma type	Concomitant treatment
1	M	16	2	A.P.	I
2	F	17	8	A.S.	I
3	M	17	1	A.S.	I
4	M	18	3	A.P.	—
5	M	14	0	A.P.	I
6	F	35	10	N.A.	—
7	M	55	5	A.S.	I
8	M	44	3	A.S.	I
9	F	40	1	A.P.	$\beta_2 + I$
10	F	43	0	NA + AI	C + β_2
11	F	53	12	N.A.	C + β_2
12	F	55	4	N.A.	C + $\beta_2 + T$
13	F	51	13	N.A.	C + T

Placebo group					
Patient No.	Sex	Age (years)	Baseline FEV ₁ variation 1st–2nd test (%)	Asthma type	Concomitant treatment
1	F	21	5	A.S.	I
2	F	16	5	A.S.	I
3	F	25	3	A.P.	T
4	F	25	6	A.S.	I
5	F	30	4	A.S.	I
6	F	42	12	A.P.	$\beta_2 + T + I$
7	F	38	2	A.P.	T
8	M	49	5	A.P.	B + β_2
9	F	52	3	A.S.	I
10	M	40	5	A.P.	$\beta_2 + T$
11	F	54	0	N.A.	$\beta_2 + T$
12	F	38	5	N.A.	$\beta_2 + \beta_2 + T$
13	F	43	12	N.A.	T
14	F	42	3	NA + AI	C + β_2

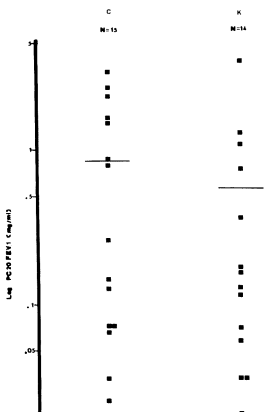


Fig. 3. Individual values of PC₂₀FEV₁ in mg/ml histamine (see histamine challenge test) in disodium cromoglycate (C) and ketotifen (K) groups. Horizontal lines: mean values. Note the wide and similar histamine sensitivity in both groups.

A logarithmic dose-response curve is then plotted, taking as BH parameter the histamine concentration which produces a 20% FEV₁ fall (PC₂₀ FEV₁ histamine, mg/ml). We obtained Δ PC₂₀ by the ratio:

$$\frac{\text{posttreatment PC}_{20} \text{ value}}{\text{pretreatment PC}_{20} \text{ value}}$$

Two reproducibility tests were conducted at intervals over 1–8 weeks on nine asthmatics (age 30.9 ± 15.9 years) who had not been included in the study. The initial values in this group of asthmatics were: FEV₁ (percentage of predicted) $79.1 \pm 11.7\%$ and PC₂₀ FEV₁ 1.02 ± 1.5 mg/ml.

Statistical analysis

The following tests were used: Paired-t test for reproducibility, variance analysis for PC₂₀ homogeneity in all treatment groups, multiple comparison Newman-Keuls test for Δ PC₂₀ data obtained with different treatments, and two-way variance analysis for interactions between treatments and age group, type of asthma or baseline level of BH.

RESULTS

Reproducibility

No significant differences were shown between the first and second tests ($P > 0.05$). The confidence interval at 99% from Δ PC₂₀ was 0.63–1.57 (Table 3).

Treatments

Baseline level of BH (PC₂₀ FEV₁) in all samples showed no significant difference (Figs. 3, 4).

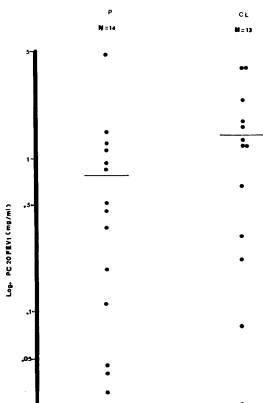


Fig. 4. Individual values of PC₂₀FEV₁ in mg/ml histamine (see histamine challenge test) in placebo (P) and clemastine (CL) groups. Horizontal lines: mean values. As in Fig. 3, both samples display a matched histamine responsiveness.

Table 3

Reproducibility test accomplished in nine patients outside the study. Time lapse between the two tests was more than 1 week. Observe how Δ PC₂₀ data varies near around the unity, suggesting an acceptable technical variation

Patient No.	1	2	3	4	5	6	7	8	9
1st PC ₂₀ mg/ml	2.00	4.50	0.04	0.17	1.25	0.50	0.02	0.57	0.06
2nd PC ₂₀ mg/ml	2.00	6.50	0.02	0.13	1.05	0.37	0.05	0.87	0.07
Δ PC ₂₀ mg/ml	1.00	1.40	0.50	0.80	0.80	0.70	2.50	1.50	1.20

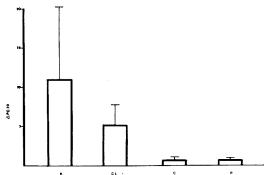


Fig. 5. Columns diagram of PC_{20} gradient (ΔPC_{20}) from each treatment. Vertical bars: 1 SD. K: Ketotifen, Cl: Clemastine, C: Disodium cromoglycate, P: Placebo. Note the wide data dispersion in the ketotifen sample; however, this did not differ significantly from the clemastine sample. PC_{20} changes after disodium cromoglycate and placebo were no different.

ΔPC_{20} values for each treatment are shown in Fig. 5. In order to unmask cumulative type I statistical error resulting from single pairs comparison, we applied the multiple comparison test (Newman-Keuls). The results showed that only the ketotifen group differed significantly from placebo ($P < 0.05$). To assess whether this difference was due to a ketotifen anti- H_1 action, we challenged an additional group with clemastine for 1 week. The results showed no significant difference between ketotifen group (8-week treatment) and clemastine group (1-week treatment). On the other hand, analysis of interactions among treatments and age groups (15–25, 26–40 and 41–55 years) showed that age had no significant influence on the results, either alone or in association with the treatment employed. None of the treatment groups was significantly influenced by type of asthma. However, a mutual influence existed between the baseline value of PC_{20} and treatment ($P < 0.05$).

DISCUSSION

The 2-month treatment with DSCG or ketotifen showed that a change in the inhaled histamine logarithm dose-response curve was more effec-

tively achieved with ketotifen than placebo, although no different from that achieved by a 1-week course of oral clemastine.

Surprisingly, an 8-week course of inhaled DSCG at therapeutic dosages fails to reach significant difference in relation to placebo in patients with similar age, type of asthma and a wide range of BH. Cockcroft et al. (10) obtained similar results in 21 asthmatics after 1 week of DSCG. Similarly, Kang et al. (25), in a study of 19 patients with extrinsic asthma, found no significant changes on challenges with inhaled or infused histamine, using only one dose of DSCG. Other studies (14, 27, 32, 34, 36) have also reported poor results with single DSCG doses.

In contrast, Woenne et al. (43), using a single DSCG dose, attained positive effect in four of 13 extrinsic asthmatic children. Kerr et al. (26) reported a slight inhibition of pulmonary function changes induced by intravenous histamine in 10 of 10 asthmatics, also with a single DSCG dose.

Positive results have been claimed with DSCG in histamine-induced bronchospasm, but these findings, however, are obscured by concurrent use of bronchodilators and the lack of control and reproducibility groups (1, 2, 15). There have been results analogous to ours concerning ketotifen. Thus, Mattson et al. (29), using a single oral dose of ketotifen, reported a significant protecting effect on histamine challenge in 24 extrinsic asthmatics. This effect did not increase after 4 weeks' treatment. Wüthrich et al. (45) observed similar results with short-term ketotifen. Beumer (4) found an inhibitory effect 4 weeks after ketotifen treatment. In accordance with this, Davies and Phillips et al. (14, 36) recently detected a parallel shift on the histamine dose-response curve with either inhaled ketotifen or inhaled clemastine.

During our study, one patient was excluded because her good results were attributed to tricyclic antidepressants. These drugs possess a powerful antihistaminic effect *in vivo* and *in vitro*, even higher than that of conventional antihistamines (41).

With other nonhistamine pharmacologic agents, Ryo et al. (38) found no difference be-

tween DSCG and placebo in adult patients. Fabri et al. (16) found a slight difference between DSCG and placebo in eight adult asthmatics with carbachol-induced bronchoconstriction. In another study (43) four of 17 extrinsic asthmatic children were partially protected against methacholine challenge after a single DSCG dose. Griffin et al. (20), using the methacholine test, found no difference between DSCG and placebo, but on challenging with cold air DSCG was more effective after the 2nd week. With regard to ketotifen and tests with nonhistamine pharmacologic agents, the previous results although disagreeing, are inconclusive (18, 30, 45).

In view of non-homogeneous previous trials (3, 5, 35) and our results, the ability of DSCG to inhibit early and late responses to allergen challenge suggests that its short effect on non-specific BH, using pharmacologic stimuli, could be due to the complexity of that phenomenon. Mediator release or production occurs through either immunologic or non-immunologic mechanisms and, together with such intrinsic factors as autonomic imbalance or airways muscle dysfunction, make up the BH puzzle. Thus, it is hardly likely that a single drug controls all these factors. Moreover, the degree of protection with DSCG against allergen challenge in extrinsic asthmatics varies individually and in some asthmatics is more or less ineffective (38).

Thus, the end result of natural or experimental allergen-induced bronchoconstriction depends not only on the allergen dose inhaled and the degree of sensitization, but also on the bronchial reactivity to several mediators released through the antigen-antibody interaction (6).

Ketotifen seems to modify nonspecific BH and allergen-induced bronchoconstriction mainly through its powerful antihistamine action. H_1 antagonist drugs have proved to be clinically ineffective by the oral route, although they act as bronchodilators when inhaled (31, 44).

In conclusion, we consider that both of the antiallergic drugs play only a moderate role in asthmatic syndrome therapy and have a slight effect on nonspecific BH in a limited number of patients on long-term treatment.

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Address:

F. Gozalo Requies, M.D.

C/Maiquez, 20

28009 Madrid

Spain

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