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Effects of long-term treatment with inhaled cromoglycate and budesonide on bronchial hyperresponsiveness in patients with allergic asthma

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ABSTRACT: Twenty two allergic patients with bronchial asthma completed this study. Effects of long-term treatment with inhaled cromoglycate 4×2 mg·day^{-1} were compared to the effects of inhaled budesonide 4×0.1 mg·day^{-1} on symptoms, additional β_2-agonist use, lung function and bronchial hyperresponsiveness measured by the provocation concentration of histamine producing a 20% fall in forced expiratory volume in one second (FEV_1) (PC_{20} histamine) and exercise-induced fall in FEV_1. The study was carried out in a double-blind way with a randomized crossover design using a double-dummy technique. After a single-blind placebo period, the two active treatment periods of 6 weeks were separated by a single-blind placebo period. Symptom score and β_2-agonist use decreased during both active treatment periods, which showed no mutual differences. Morning and evening peak expiratory flow rates were significantly higher during treatment with budesonide *versus* placebo ($p<0.01$ and $p<0.001$), and also *versus* cromoglycate ($p<0.02$ and $p<0.05$). FEV_1 showed improvement after a 6 week treatment with budesonide *versus* placebo ($p<0.05$), although there was no significant difference between the two active treatments. PC_{20} histamine did not change during treatment with cromoglycate. Budesonide showed a significant increase in PC_{20} histamine *versus* placebo ($p<0.05$) and was marginally significantly better than cromoglycate ($p=0.05$). Exercise-induced fall in FEV_1 was not changed by cromoglycate, but improved significantly during budesonide in comparison with placebo ($p<0.01$) and also with cromoglycate ($p<0.001$). Both cromoglycate and budesonide showed anti-asthmatic effects. Improvement in lung function was more pronounced during treatment with budesonide. Budesonide decreased bronchial hyperresponsiveness, expressed by PC_{20} histamine as well as exercise-induced fall in FEV_1, whereas cromoglycate did not.

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One of the main features of bronchial asthma, with or without allergy, is an increased bronchial responsiveness to nonspecific stimuli such as cold air, smoke, exercise and to pharmacological agents such as histamine and methacholine. The presence and degree of bronchial hyperresponsiveness can be demonstrated by assessing the broncho-obstructive response to these various stimuli in the lung function laboratory. Nowadays, the provocation test with inhaled histamine is well standardized and can be used to measure bronchial hyperresponsiveness; furthermore, there is a relationship between this measurement and the severity of the asthmatic symptoms [1, 2].

Pharmacological treatment of patients with bronchial asthma should be directed at relieving the actual bronchoconstriction and, if possible, at reducing the increased bronchial responsiveness. Examples of prophylactic drugs that do not have direct bronchodilating effects are cromoglycate and corticosteroids. A single dose of inhaled cromoglycate, prior to allergen exposure, prevents both early rapid and late sustained phase bronchoconstrictive reactions [3, 4]. A single dose of inhaled corticosteroids, prior to allergen exposure, mainly prevents the late phase bronchoconstrictive reaction [4, 5]. During the late phase asthmatic reaction inflammatory changes develop in the bronchial wall [6]. An increase in bronchial hyperresponsiveness to nonspecific stimuli is seen when a late phase asthmatic reaction occurs after allergen exposure, an increase that sometimes lasts several days [5, 7].

As both inhaled cromoglycate and inhaled corticosteroids prevent the late phase asthmatic reaction, an influence of these drugs on bronchial hyperresponsiveness may be expected. Studies of long-term treatment of bronchial hyperresponsiveness with inhaled cromoglycate show no clear and partially conflicting results

[8, 9]. Budesonide, a recently developed corticosteroid for inhalation use, decreases bronchial hyperresponsiveness during long-term treatment in allergic children with bronchial asthma [10, 11].

The aim of this comparative study was to elucidate the effects of inhaled cromoglycate and budesonide on pulmonary function and bronchial hyperresponsiveness during long-term treatment in adult allergic patients with bronchial asthma. The bronchial hyperresponsiveness was assessed by two methods: the exercise provocation test as an example of a physiological challenge and the histamine provocation test as a standard pharmacological challenge.

Patients and methods

Patient characteristics

Patient characteristics are listed in table 1. Thirty one patients (19 M, 12 F) participated in the study, aged 15–47 yrs (mean age 27 yrs). One patient (No. 20, 26) participated twice. Basal forced expiratory volume in one second (FEV_1) had to be ≥50% of the predicted value [12], range: 51–106% (mean 74%). Acute reversibility of FEV_1 had to be more than 15% in response to an inhaled $ß_2$-agonist. Airway hyperresponsiveness was expressed as the provocation dose of histamine producing a 20% fall in FEV_1 (PC_{20} histamine) which was measured by means of the COCKCROFT and HARGREAVE method [1] and had to be ≤8 $mg \cdot ml^{-1}$, range: responsive to saline up to 2 $mg \cdot ml^{-1}$ histamine (geometric mean 0.09 $mg \cdot ml^{-1}$). All the patients had an allergic constitution. Allergy was demonstrated by clearly positive intracutaneous skin tests. These tests had to be positive with respect to the house dust mite allergen and two other common inhalational allergens corresponding with the case history. The skin test was considered clearly positive when the wheal reaction that emerged 20 min after the injection of the allergen concerned, was equal to or larger than the wheal reaction of histamine, which served as a control. The skin tests had to be negative for seasonal allergens like tree and grass pollen (Pharmalgen® 100 $BU \cdot ml^{-1}$ standardized extracts, Pharmacia AB, Uppsala, Sweden). Current medication to control symptoms consisted of inhaled corticosteroids,

Table 1. – Patient characteristics

n	Sex	Age yrs	FEV_1 %pred	PC_{20} $mg \cdot ml^{-1}$	Previous medication	Smoking history
1	M	32	103	–	s b	-
2	F	28	78	0.20	c b	-
3	M	30	71	2.00	b t	+
4	M	35	83	0.27	s b	-
5	F	23	68	0.57	c b	-
6	F	30	94	0.25	c b	-
7	F	34	65	0.04	s c b	-
8	M	33	78	0.34	s b	+
9	M	27	79	S	b	-
10	M	30	60	0.04	s b	-
11	F	27	106	0.11	s c b	-
12	M	29	82	0.16	s b	+
13	M	47	84	0.07	c b	-
14	F	28	78	0.04	s b	-
15	M	31	89	1.10	c b	-
16	F	20	83	0.16	b t	+
17	M	17	83	S	s b	-
18	F	20	53	S	s b	-
19	F	35	89	–	s c b	-
20*	M	24	70	0.39	c b	+
21	M	16	73	0.62	s c b	-
22	M	15	54	–	s c b	-
23	M	22	60	0.05	s c b	-
24	M	35	51	0.05	c b	-
25	F	23	57	0.21	s b	+
26*	M	24	70	–	c b	+
27	M	24	71	0.36	s b	-
28	M	34	67	0.18	s b	-
29	M	20	66	0.20	c b	-
30	F	16	89	S	c b	-
31	F	37	59	0.07	c b	-
32	M	18	90	S	s c b	-
Mean		27	74	0.09		

*: the same patient; S: responsive to 0.9% saline inhalation; FEV_1: forced expiratory volume in one second; PC_{20}: provocation concentration of histamine causing a 20% fall in FEV_1, measured after 2 weeks placebo; b: inhaled $ß_2$-sympathomimetics; c: inhaled cromoglycate; t: oral theophylline; s: inhaled steroids; – (PC_{20} column): histamine provocation test not performed (patient withdrawal during placebo treatment).

inhaled cromoglycate, inhaled β_2-sympathomimetics and sustained-release theophylline preparations taken orally. All these treatments were discontinued at the start of the study.

Excluded were patients who were pregnant, patients with serious concomitant diseases, recent airway infections (<8 weeks), recent systemic oral or intravenous treatment with corticosteroids (<12 months) and those not being able to handle a peak expiratory flow meter and/or metered-dose inhalers or to fill out diary cards.

Study design

The study was carried out in a double-blind way with a randomized cross over design using a double-dummy technique. The whole study lasted 17 weeks. First, there was a single-blind washout placebo period (I) of 2 weeks, followed by two periods of active treatment, each lasting 6 weeks, separated by a single-blind placebo period (II) of 3 weeks (fig. 1).

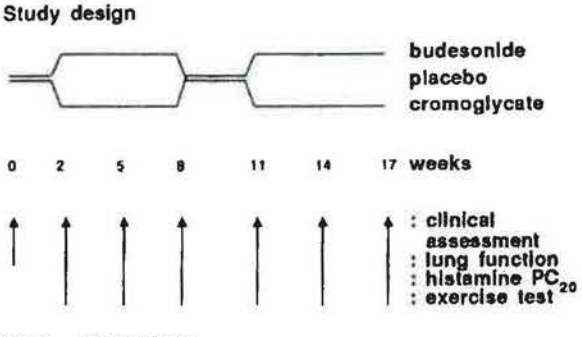

Fig. 1. – Study design.

Study drugs

During the study only the following drugs were used:
1) Cromoglycate metered-dose inhalers (1 mg per actuation) and placebo inhalers of identical appearance (Fisons Ltd, Loughborough, UK);
2) Budesonide metered-dose inhalers (0.05 mg per actuation) and placebo inhalers of identical appearance (Draco AB, Lund, Sweden);
3) As rescue medication, rimiterol metered-dose inhalers (0.2 mg per actuation, Riker-3M Nederland BV, Zoeterwoude, The Netherlands) or salbutamol dry powder inhalations (0.2 mg per capsule, Glaxo BV, Nieuwegein, The Netherlands) could be used.

Throughout the 17 weeks of the study the patients were instructed to use two actuations of both cromoglycate/placebo and budesonide/placebo inhalers four times daily. During the periods of active treatment the patients thus inhaled 8 mg cromoglycate daily or 0.4 mg budesonide daily. During the whole study rimiterol or salbutamol could be used as rescue medication if necessary.

Both the use of the study drugs and the rescue medication were recorded on diary cards. The study drug-canisters were weighed afterwards, to estimate compliance.

Measurements

Visit 1. At the beginning of the study lung function indices were measured in the morning after withholding bronchodilators for a period of at least 8 h, and after refraining from vigorous physical exercise. Flow-volume equipment was used (Pneumoscreen, Jaeger), the best values of three attempts were evaluated. Next the single-blind placebo period started for 2 weeks.

Every day throughout the period of 17 weeks of the study the patients filled out diary cards concerning symptom scores, morning and evening peak expiratory flow rate measurements and the use of rescue medication. Peak expiratory flow rate was measured with a Wright peak flow mini-meter (Airmed, Clement Clarke Int, Ltd, UK). The best of three attempts before using a β_2-agonist was recorded daily. Pulmonary symptoms such as dyspnoea, wheeze and cough were recorded daily, using a 0–5 scale (0=no to 5=severe symptoms). The quantity of expectoration was also recorded on a 0–5 scale (0=none to 5=at least one coffee cup filled).

Clinical assessments were all made by the same investigator (author J.M.) making use of a standard questionnaire. Specific questions were asked about the severity of day-time and night-time complaints of dyspnoea, wheeze, cough and about the severity of exercise- and smoke-induced dyspnoea using a 0–3 scale (0=none to 3=severe). Efficacy and side-effects were also recorded. Signs of infection of the airways during the study were considered a reason for withdrawal.

Visits 2–7. For visit 2, after 2 weeks, and for the other visits, after every third week, the patients arrived at the out-patient clinic every morning at the same time as for visit 1, refraining from vigorous physical exercise. No medication whatsoever was allowed for a period of 8 h before each visit.

Baseline lung function was measured followed by a histamine provocation test according to the COCKCROFT and HARGREAVE method [1]. After reaching >20% fall in FEV_1, PC_{20} histamine was calculated by linear interpolation of the log-histamine concentration *versus* ΔFEV_1 response curve. For statistical reasons, PC_{20} was arbitrarily set at 0.02 $mg \cdot ml^{-1}$ in the calculations, if a >20% fall in FEV_1 was seen after inhalation of the lowest histamine concentration (0.03 $mg \cdot ml^{-1}$). Likewise, if a >20% fall in FEV_1 was already seen after inhaling saline 0.9%, PC_{20} was set at 0.01 $mg \cdot ml^{-1}$.

After a pause of at least 30 min and recovery of FEV_1 to at least ≥95% of baseline FEV_1, an exercise provocation test was performed. After getting accustomed to the treadmill for 30 s at a speed of 3 $km \cdot h^{-1}$, the speed was raised until the heart rate reached 80% or more of the age-related predicted maximum heart rate (220 minus age in yrs) per min. At this level the

Table 2. – Effects of treatment with placebo, cromoglycate and budesonide on symptom score, peak expiratory flow rate and β_2-agonist use (n=22, mean values)

	Placebo		Cromoglycate 4x2 mg		Budesonide 4x0.1 mg	
	I	II				
Wks	1+2	2+3	2+3	5+6	2+3	5+6
Diary card scores (0–5)						
Dyspnoea	1.42	0.94	0.74***	0.69***	0.61***	0.64***
Wheeze	0.77	0.52	0.46**	0.42***	0.33***	0.34**
Cough	0.65	0.54	0.60	0.50	0.40*	0.50
Sputum production	0.67	0.46	0.54	0.37**	0.39*	0.45
Morning PEFR $l \cdot min^{-1}$	448	463	473*	467	482**	489**
Evening PEFR $l \cdot min^{-1}$	483	496	504**	504*	520***	522***
PEFR drop/night $l \cdot min^{-1}$	33	33	30	37	37	33
β_2-agonist use inhalations·day^{-1}	2.81	2.34	1.74*	1.78*	1.28**	1.48*

PEFR: peak expiratory flow rate; *: p<0.05; **: p<0.01; ***: p<0.001; all significance values compared to placebo I.

exercise lasted 6 min. After that 1 min was taken to reduce the speed of the treadmill. Ventilatory capacity was measured before the test and 1, 3, 6, 9, 12 and 15 min after completing the exercise. The largest fall in FEV_1, expressed as percentage fall in FEV_1 *versus* the initial value of FEV_1, was used for calculations. The test was performed under constant room temperature (19±1°C) and relative humidity conditions (60±10%).

Statistical analysis

Paired t-tests were used to compare the spirometric parameters, the exercise-induced fall in lung function and the peak expiratory flow rate recordings at home. Paired t-tests and non-parametric tests (Wilcoxon) were used to compare the $^{10}\log PC_{20}$ histamine, clinical assessment scores and symptoms. The results after 3 and 6 weeks of active therapy were compared to the results after the first placebo period. The diary card parameters were averaged taking the last 2 weeks of each drug or placebo period.

Two-tailed p values below 0.05 were considered statistically significant.

Ethical considerations

The study was approved by the local Medical Ethics Committee. Informed consent was obtained from each patient after presenting a written outline of the study summarizing the protocol.

Results

Twenty two patients of the 31 who entered, completed the whole study. Nine patients were withdrawn from the study. One person entered and was withdrawn twice due to respiratory tract infection, once during treatment with cromoglycate, once during treatment with placebo. One other patient dropped out during treatment with cromoglycate due to respiratory tract infection. Three other patients dropped out during treatment with placebo due to worsening of their asthma, intolerance and non-compliance. Four patients were withdrawn from the study during treatment with budesonide because of pregnancy (1), respiratory tract infection (2) and deterioration of asthma (1). The results after the two placebo periods and the results after treatment with cromoglycate and budesonide are presented for the 22 patients who completed the study.

The results obtained at the end of the two placebo periods were comparable. The results measured during treatment with cromoglycate and budesonide were compared with the values found after the first placebo period. The exercise-induced fall in lung function was more pronounced after the second placebo period than after the first placebo period (24.8% *vs* 16.7%, p<0.05). This increased fall in lung function, however, was not related to the type of treatment given before this placebo period. The changes in lung function after exercise were compared with the placebo values obtained after placebo treatment given just before the drug concerned; these placebo values did not show any statistically significant differences

Daily symptom scores, peak expiratory flow rate measurements and the use of rescue medication were collected from the diary cards (table 2). Symptom scores during the two active treatment periods were decreased in comparison to treatment with placebo. The differences between the effects of the two drugs were small and not statistically significant.

During the first 3 weeks of treatment with cromoglycate, morning and evening peak expiratory flow rates were significantly higher in comparison to treatment with placebo (p<0.05 and p<0.01, respectively). Only the evening peak expiratory flow rate remained significantly higher during the second 3 weeks (p<0.05). During the first as well as the second 3 weeks of treatment with budesonide, both morning (p<0.01) and evening peak expiratory flow rate (p<0.001) were

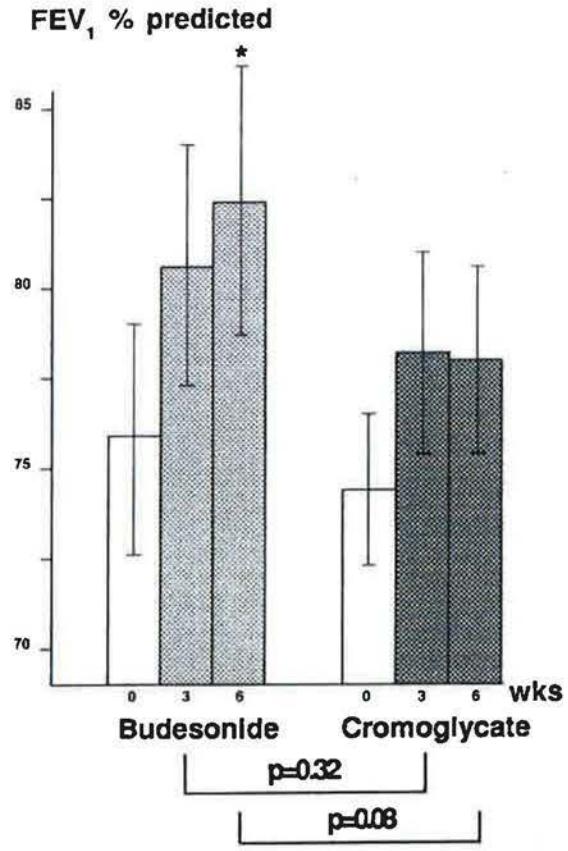

Fig. 2. – Effects of treatment with placebo (0), cromoglycate (4x2 mg) and budesonide (4x0.1 mg) on forced expiratory volume in one second (FEV_1) as percentage predicted (n=22, mean±SE, *: $p<0.05$ *vs* placebo).

significantly higher than during treatment with placebo. Statistically, the evening peak expiratory flow rate values after the first 3 weeks of treatment (p=0.02) and both the morning (p=0.01) and evening peak expiratory flow rate (p=0.03) after 6 weeks of treatment were significantly higher during treatment with budesonide than during treatment with cromoglycate.

The use of rescue medication with a $ß_2$-agonist was low throughout the study and was on average 1.38 inhalation·day^{-1} during treatment with budesonide and 1.76 inhalations·day^{-1} during treatment with cromoglycate. Statistically, the difference between the two active treatment periods was not significant. However, during the use of both these drugs rescue medication was used less frequently in comparison to the use of rescue medication during treatment with placebo (2.81 inhalations·day^{-1}, $p<0.05$).

Clinical assessment (table 3) was performed by the same investigator each visit. Complaints were less severe during the two active treatment periods than during the placebo periods. Nocturnal symptoms were minimal throughout the whole study and showed no significant differences between placebo and active drug treatment periods. Treatment with budesonide was significantly better than with cromoglycate after 3 weeks of treatment for day-time dyspnoea (p=0.03), wheeze (p=0.049), cough (p=0.04) and exercise-induced symptoms (p=0.02). However, this could no longer be observed after 6 weeks of treatment. Only exercise-induced symptoms remained significantly decreased during treatment with budesonide compared to treatment with cromoglycate after 6 weeks ($p<0.05$).

Baseline FEV_1 (fig. 2) showed no change during treatment with cromoglycate. Treatment with budesonide caused a significant improvement in FEV_1 after 6 weeks of treatment ($p<0.05$). The differences between the effects of the two drugs were small and not statistically significant.

PC_{20} histamine (fig. 3) showed no change during treatment with cromoglycate. Treatment with budesonide caused a significant increase after 3 weeks ($p<0.01$) and 6 weeks ($p<0.05$). Using the non-parametric Wilcoxon's signed rank test, the budesonide-induced effect is significant ($p<0.01$) both after 3 and 6 weeks. The difference between treatment with budesonide and cromoglycate was marginally statistically significant after 3 weeks (p=0.07) and after 6 weeks (p=0.05).

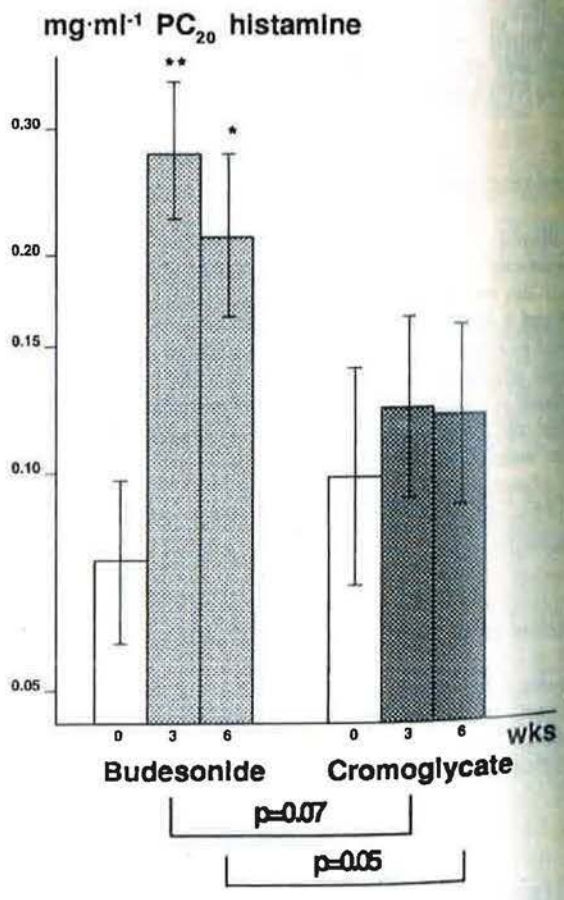

Fig. 3. – Effects of treatment with placebo (o), cromoglycate (4x2 mg) and budesonide (4x0.1 mg) on the provocation concentration of histamine producing a 20% fall in forced expiratory volume in one second (PC_{20} histamine) (n=22, geometric mean±SE, *: $p<0.05$ *vs* placebo; **: $p<0.01$ *vs* placebo.

Table 3. – Effects of treatment with placebo, cromoglycate and budesonide on clinical assessment score (n=22, mean values)

	Placebo		Cromoglycate 4x2 mg		Budesonide 4x0.1 mg	
	I	II				
Wks	1+2	2+3	2+3	5+6	2+3	5+6
Clinical assessment (0–3)						
Day-time dyspnoea	1.41	1.14	0.91**	0.73**	0.55***	0.52**
Day-time wheeze	1.00	0.82	0.64*	0.64	0.32**	0.33**
Day-time cough	0.64	0.64	0.46	0.32*	0.27**	0.38
Exercise symptoms	1.09	0.96	0.82	0.64*	0.41***	0.29**

*: p<0.05; **: p<0.01; ***: p<0.001; all significance values compared to placebo I.

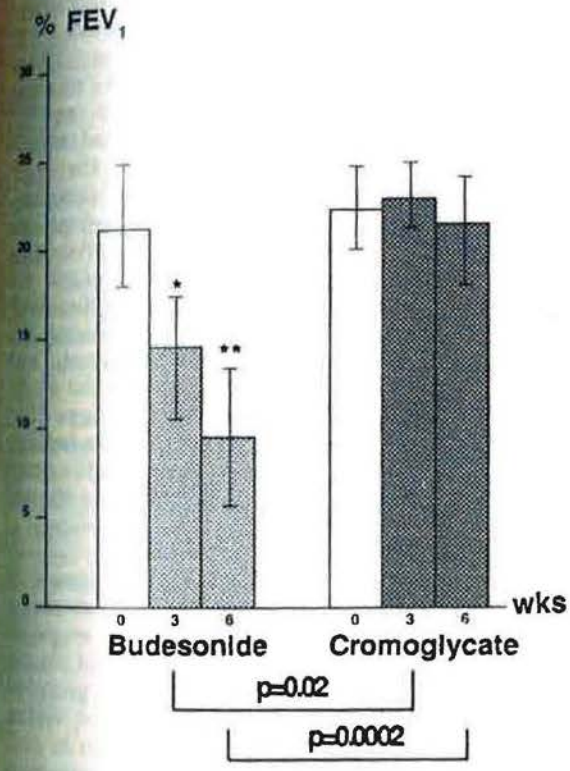

Fig. 4. – Effects of treatment with placebo (0), cromoglycate (4x2 mg) and budesonide (4x0.1 mg) on exercise-induced fall in forced expiratory volume in one second. (FEV_1) (n=22, mean±SE, *: p<0.05 *vs* placebo; **: p<0.01 *vs* placebo).

Treatment-induced effects on the exercise-induced fall in FEV_1 were compared with placebo measurements just before the drug concerned was to be used (fig. 4). During treatment with cromoglycate no statistically significant differences were seen compared with placebo treatment. Budesonide caused a statistically significant decrease in the exercise-induced fall in FEV_1 both after 3 weeks (p<0.05) and after 6 weeks (p<0.01) compared with placebo values. The difference between the two drugs is statistically significant both after 3 weeks (p=0.02) and after 6 weeks (p=0.0002), in favour of budesonide.

With regard to patient compliance, an average of 15 inhalations·day^{-1} of the study drugs was recorded by the patients throughout the study. Assessed by weighing the canisters, the average number of inhalations actually taken was 7.0 for cromoglycate and 7.4 for budesonide (88% and 93% of the number of inhalations prescribed). In only 4 of the 44 treatment periods was the use below 6 inhalations·day^{-1}.

Side-effects were reported by 10 of the 31 patients. In most cases these were mild complaints of cough, hoarseness and/or dyspnoea occurring shortly after the use of the trial metered-dose inhalers, lasting 10–30 min. In only one patient (No. 22) was it more than mild and in fact was enough reason to withdraw this patient during the first placebo period. Cough was mentioned by one patient throughout the study, but this was no reason for withdrawal. Hoarseness was reported by 2 patients during placebo, by 2 patients during treatment with cromoglycate and by 4 patients during treatment with budesonide. Dyspnoea after inhalation of the study drugs was reported by 4 patients during treatment with placebo, 3 patients during treatment with cromoglycate and one patient during treatment with budesonide. No significant differences were observed between the two active drug periods. Physical examination and pharyngeal swabs showed no abnormalities within these patients.

The patient's preference was assessed at the end of the study as no, slight or strong preference for a certain period. In 9 patients no preference could be assessed. In 7 patients there was a slight preference, 3 in favour of cromoglycate, 4 in favour of budesonide. Six patients mentioned a strong preference, all in favour of budesonide (p<0.05, Wilcoxon's signed rank test).

Discussion

In this study inhaled cromoglycate showed some improvement in symptom scores, evening peak expiratory flow rate and additional β_2-agonist use. Clinical assessment scores showed a decrease in day-time dyspnoea, cough and exercise-induced symptoms. However, baseline FEV_1 and the severity of bronchial hyperresponsiveness, as assessed by PC_{20} histamine and

the exercise-induced fall in FEV_1, did not change.

Inhaled budesonide showed a more pronounced improvement of symptom scores and of both evening and morning peak expiratory flow rates. Additional β_2-agonist use decreased, and clinical assessment scores showed fewer complaints. Treatment with budesonide, in contrast with cromoglycate, showed improvement of baseline FEV_1 and a decrease in severity of bronchial hyperresponsiveness, as assessed by measuring both PC_{20} histamine and exercise-induced fall in FEV_1.

Inhaled cromoglycate given in a single dose prior to allergen exposure, prevents both early rapid phase and late phase bronchoconstriction [3]. Exercise-induced bronchoconstriction is largely prevented when inhaled cromoglycate is given prior to exercise [13]. However, no influence on histamine-induced bronchoconstriction was observed [14].

During the long-term treatment with cromoglycate in our study the patients were not allowed to use the morning dose of the study drug nor the rescue medication on the test day. The short-term prophylactic effects of cromoglycate had already been washed out by then [15]. If, however, the long-term treatment with cromoglycate had any effect on bronchial hyperresponsiveness, one would expect effects on histamine tolerance and possibly also on exercise-induced bronchoconstriction. However, no such effects were seen, which implies that the effects of cromoglycate are of short duration and the end-organ response is not modulated. A recent report [8] also showed no change in bronchial hyperresponsiveness, as assessed by PC_{20} histamine, during continuous treatment with cromoglycate in 48 adult asthmatic patients of whom 41 were also allergic, proved by skin prick tests.

Inhaled corticosteroids given in a single dose prior to allergen exposure mainly prevents the late phase bronchoconstriction [4, 5]. Inhaled corticosteroids showed no protection against bronchoconstriction when given immediately before histamine inhalation [16] or exercise [17].

The long-term treatment with inhaled corticosteroids in our study showed a clear change in bronchial hyperresponsiveness, expressed both by an increased histamine and exercise tolerance. Other studies have also shown effects on PC_{20} histamine [10, 18] and exercise-induced bronchoconstriction [11]. Corticosteroids, but also cromoglycate, prevent late asthmatic responses and allergen-induced increases in airway responsiveness [3, 4, 19]. It is generally accepted that one of the effects of cromoglycate is to block the release of mediators from mast cells and therefore it seems to be a prophylactic medication and will probably only influence symptoms brought about by current allergen exposure, or mediator release caused otherwise. Corticosteroids by being non-specifically anti-inflammatory may improve airway hyperresponsiveness to some extent under all circumstances. Long-term treatment with inhaled corticosteroids also prevents early asthmatic responses [19]. These effects induced by corticosteroid treatment probably indicate both a mast cell stabilizing effect during long-term treatment and a modulation of the end-organ responsiveness due to anti-inflammatory effects in the bronchial mucosa [20]. With regard to the evaluation of the prophylactic aspects of action of corticosteroid treatment *in vivo*, further studies are needed, *i.e.* to compare the protective effects of cromoglycate and inhaled corticosteroids on seasonal increases in airway responsiveness in patients who show no increased responsiveness out of season.

Three other studies have been published, in which treatment with inhaled cromoglycate was compared to treatment with inhaled corticosteroids. A study by RAK and LÖWHAGEN [21] compared cromoglycate 20 mg *t.i.d.* with budesonide 0.40 mg *t.i.d.* in adult patients with bronchial asthma without allergy. They reported some protective effects of both treatments on PC_{20} histamine. A study by SVENDSEN *et al.* [9] compared cromoglycate 2 mg *q.i.d.* with beclomethasone dipropionate 0.40 mg *b.i.d.* The inhaled corticosteroid proved to be effective on lung function (increase in FEV_1) as well as PC_{20} histamine (a 34% increase). In the first period, after 4 weeks of therapy, cromoglycate showed the same effect on PC_{20} histamine as beclomethasone dipropionate, but not after 8 weeks of treatment. Cromoglycate showed no effect on PC_{20} histamine when given as a second treatment. Because there was no wash out period between the active treatment periods, this study is difficult to interpret. The study by OSTERGAARD and PEDERSEN [22] compared inhaled cromoglycate and budesonide in the same dose as we used in our study, in children with bronchial asthma with allergy. They found no effects of cromoglycate on exercise-induced bronchoconstriction but a pronounced favourable effect of budesonide. In their study PC_{20} histamine showed small, but statistically significant changes, without a significant difference between the two drugs.

Data are emerging to suggest that an increase in airway responsiveness induced by allergens can persist for days, weeks or even longer [7, 23]. The prognosis of patients suffering from bronchial asthma and chronic obstructive pulmonary disease (COPD) probably depends on the degree and the reversibility of airflow limitation [24–26] which in turn seem, at least in part, related to the degree of bronchial hyperresponsiveness [2]. Therefore, pharmacological treatment of patients with bronchial asthma and COPD should not only be directed at relieving actual bronchoconstriction, but also, if possible, at decreasing airway hyperresponsiveness.

The present study has shown clinically important anti-asthmatic effects and a decrease in bronchial hyperresponsiveness during treatment with inhaled budesonide, without serious side-effects occurring. These findings correspond with the patients' preference for treatment with budesonide. With regard to adrenal function, others have already shown that in the usual dose *e.g.* 400 μg budesonide daily, as was used in this study, no such side-effect exists or seems to be important [32]. A relationship between symptoms and measurement of lung function and airway hyperresponsiveness has been observed [2, 27, 28]. It remains, however, difficult to

predict current symptoms of asthma from a measurement of airway hyperresponsiveness [29]. Patients can be hyperreactive without complaints or symptoms. Also the degree of hyperresponsiveness is related to the degree of airflow obstruction, but again patients can be hyperreactive without showing airflow limitation at a certain moment. Therefore, in the follow-up of asthmatic patients the recording of symptoms is of some value but this follow-up should at least include the measurement of lung function indices, not only FEV_1 but also peak expiratory flow rate which provides more reliable data due to the frequency of measurements [30], and preferably also measurement of airway hyperresponsiveness. The correlation between the degree of exercise-induced bronchoconstriction and of histamine/methacholine-induced bronchoconstriction is variable. Exercise-induced bronchoconstriction is usually more pronounced in the more severe asthmatic patients than in those with the lowest histamine/methacholine threshold [31]. In the present study the exercise-induced fall in FEV_1 was more than halved by the treatment with budesonide. This is undoubtedly of clinical importance, and appreciated by the patient. Compliance with therapy may also be better when the patient experiences changes induced by a certain drug in more physiological laboratory tests, *e.g.* an exercise test which can become negative, rather than in a test like the histamine provocation test. Using the latter test improvements can also be seen, but PC_{20} histamine will seldom rise >8 $mg \cdot ml^{-1}$. This indicates the importance of assessing the PC_{20} histamine as a measurement of airway hyperresponsiveness and continuing disease. In exercise provocation, bronchoconstriction may still appear, it decreases, however, to a level of no clinical importance in most patients and therefore responsiveness to exercise is a very useful parameter to study the effects of pharmacological treatment of airway hyperresponsiveness.

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Effets des traitements au long cours par le cromoglycate et le budesonide en inhalation sur l'hyperréactivité bronchique, chez des patients atteints d'asthme allergique. J. Molema, C.L.A. van Herwaarden, H.Th.M. Folgering.

RÉSUMÉ: Vingt-deux patients allergiques, atteints d'asthme bronchique, ont conduit cette étude à son terme. L'on a comparé les effets d'un traitement au long cours par le cromoglycate en inhalation (4 x 2 mg/jour), à ceux du budesonide en inhalation (4 x 0.1 mg/jour) sur les symptômes, sur l'utilisation complémentaire de β_2-agonistes, sur la fonction pulmonaire et l'hyperréactivité bronchique mesurée par chute du VEMS induite par l'effort et par le PC_{20} d'histamine. L'étude a été conduite en double aveugle avec un schéma randomisé avec permutation croisée, utilisant la technique du "double-dummy". Après une période de placebo en simple aveugle, le score des symptômes et l'utilisation des β_2-agonistes ont diminué durant les deux périodes de traitement actif, qui n'ont révélé aucune différence entre elles. Les débits expiratoires de pointe du matin et du soir sont significativement plus élevés pendant le traitement au budesonide que pendant le placebo ($p<0.01$ et $p<0.001$), ainsi que vis-à-vis du cromoglycate ($p<0.02$ et $p<0.05$). Le VEMS est amélioré après un traitement de 6 semaines au budesonide par comparaison avec le placebo ($p<0.05$), quoiqu'il n'y ait pas de différence significative entre les deux traitements actifs. Le PC_{20} d'histamine ne se modifie pas au cours du traitement au cromoglycate. Par contre, le budesonide entraîne une augmentation significative du PC_{20} d'histamine par rapport au placebo ($p<0.05$) et s'avère significativement meilleur que le cromoglycate, mais de façon marginale ($p=0.05$). La chute de VEMS induite par l'effort n'est pas modifiée par le cromoglycate, mais est significativement améliorée au cours du traitement au budesonide par comparaison avec le placebo ($p<0.01$) et aussi avec le cromoglycate ($p<0.001$). Tant le cromoglycate que le budesonide ont donc manifesté des effets anti-asthmatiques. L'amélioration fonctionnelle pulmonaire est plus marquée au cours du traitement par le budesonide. Le budesonide réduit l'hyperréactivité bronchique traduite par un PC_{20} d'histamine, ainsi que la chute de VEMS provoquée par l'effort, alors que le cromoglycate ne le fait pas.
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