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Effect of inhaled beclomethasone and nedocromil sodium on bronchial hyperresponsiveness to histamine and distilled water

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ABSTRACT: In a randomized, cross-over study we compared the effects of inhaled nedocromil sodium, 4 mg *q.i.d.*, with inhaled beclomethasone dipropionate, 200 μg *q.i.d.* in 23 atopic asthmatic patients. After a 3 week single-blind placebo period, regarded as the baseline, and after 4 and 8 weeks of active treatment, drug effects were assessed with regard to bronchial hyperresponsiveness to histamine and distilled water, lung function and β_2-agonist use.

After 4 and 8 weeks of treatment, nedocromil sodium reduced the histamine responsiveness ($p<0.005$ and $p<0.0005$), but not the distilled water responsiveness, and did not improve lung function and peakflow measurements compared to baseline. After 4 and 8 weeks of treatment, beclomethasone caused a significant increase in lung function ($p<0.005$) and decrease in bronchial hyperresponsiveness to histamine ($p<0.0005$) and distilled water ($p<0.0005$) as compared to baseline. β_2-agonist use was significantly diminished after an 8 week treatment with beclomethasone, whereas nedocromil sodium had no effect.

Treatment with beclomethasone was superior to treatment with nedocromil sodium with regard to bronchial hyperresponsiveness to histamine and distilled water ($p<0.0005$ and $p<0.005$), lung function ($p=0.003$), peakflow measurements ($p<0.05$) and β_2-agonist use ($p<0.005$).

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Bronchial hyperresponsiveness to a variety of chemical, physical and pharmacological stimuli is one of the major characteristics of bronchial asthma [1, 2]. The underlying mechanism of bronchial hyperresponsiveness is still unknown, but several aspects have recently been elucidated. Disruption of the epithelial layer, inflammatory changes in the airway wall and, possibly, an imbalance in the autonomic regulation of the airway appear to contribute to the pathophysiology of bronchial hyperresponsiveness [1, 3].

The presence and the degree of bronchial hyperresponsiveness can be assessed by bronchoprovocation tests with pharmacological and physical stimuli. HARGREAVE *et al.* [4] found a correlation between the severity of asthma and the degree of bronchial hyperresponsiveness to histamine and methacholine. Nonspecific stimuli, such as exercise [5] and ultrasonically nebulized distilled water (UNDW) [6], can also be used for the assessment of bronchial hyperresponsiveness. The latter challenges are supposed to have the advantage of corresponding better with the daily exposure of the asthmatic subject to nonspecific stimuli [7].

The treatment of asthma is focused on diminishing the inflammatory process and bronchial hyperresponsiveness [8]. In a previous study, we compared the effects of sodium cromoglycate and budesonide on bronchial hyperresponsiveness in asthmatic subjects [9]. Budesonide induced a significant decrease in bronchial hyperresponsiveness to histamine and exercise, whereas sodium cromoglycate did not have such effects. Nedocromil sodium, a pyranoquinoline dicarboxylic acid derivative, has anti-inflammatory properties, as demonstrated by *in vitro* and *in vivo* experiments, and seems to be more potent than sodium cromoglycate [10]. Nedocromil sodium can inhibit early- and late-phase asthmatic responses after allergen inhalation [11], and prevents bronchoconstriction induced by inhaled SO_2 [12], cold air [13], distilled water [14], substance P [15], adenosine [16] and exercise [17]. However, the place of this drug in the treatment of asthma has not yet been defined. The aim of the present study was to investigate the effects of regularly inhaled nedocromil sodium in comparison with inhaled beclomethasone dipropionate on lung function, bronchial hyperresponsiveness to histamine and distilled water, and β_2-agonist use in allergic asthmatic subjects.

Table 1. – Patient characteristics

Subject no.	Sex	Age yrs	FEV_1 % pred	MEF_{50} % pred	MEF_{25} % pred	PD_{20} hist µmol	PD_{20} UNDW ml H_2O	Previous medication
1	F	40	100	72	78	0.05	1.4	s, b
2	F	35	85	49	41	0.05	1.0	s, b
3	F	27	68	34	39	0.50	13.7	s
4	M	26	89	74	64	0.40	0.9	s, b
5	M	22	95	110	155	0.24	10.7	s
6	F	23	87	75	53	0.09	0.6	s, b
7	F	38	82	37	37	0.12	8.2	s, b
8	M	25	51	23	23	0.002	0.6	s, c
9	M	26	89	53	61	0.09	3.6	s, b
10	F	40	72	50	62	0.19	5.3	s, b
11	M	26	101	73	63	0.24	6.2	s, b
12	M	21	63	31	18	0.002	0.1	s, bud
13	F	44	99	76	66	0.01	1.7	s, b
14	M	38	66	36	33	0.24	4.3	s, bud
15	F	32	74	56	64	0.002	0.4	s, b
16	M	17	87	55	51	0.03	9.8	s, b
17	F	19	91	68	46	0.17	2.4	s, bud
18	M	28	89	52	57	0.16	2.0	s, bud
19	F	38	98	99	83	0.03	0.7	s, b
20	F	21	100	58	54	0.004	0.5	s, b
21	M	31	71	38	42	0.17	3.4	s, bud
22	M	19	78	46	40	0.002	0.3	s, b
23	M	27	107	93	81	0.09	-	s
24	F	50	93	66	77	0.04	2.4	s, b
25	M	38	65	34	34	0.04	5.5	s, b
26	M	21	82	50	41	0.06	1.6	s, b
27	M	17	70	40	39	0.04	1.0	s, b
28	M	30	103	59	48	0.24	3.5	s
Mean		29	84	57	55	0.12	3.4	
SEM		1.7	2.7	4.0	4.9	0.02	0.7	

FEV_1: forced expiratory volume in one second; MEF_{50} and MEF_{25}: maximal expiratory flow when 50% and 25% of the forced vital capacity have to be expired; PD_{20}: provocative dose producing a 20% fall in FEV_1; UNDW: ultrasonically nebulized distilled water; s: salbutamol powder inhalation; c: cromoglycate powder inhalation; b: beclomethasone powder inhalation; bud: budesonide aerosol.

Methods

Subjects

Twenty eight nonsmoking subjects with allergic bronchial asthma [18] participated in the study. All patients were recruited from the hospital out-patient department. Some characteristics of these patients are shown in table 1. Allergy was defined as two or more positive intracutaneous skin test reactions to common airborne allergens. Patients with seasonal allergy did not participate in the study during that specific season. The pre-challenge forced expiratory volume in one second (FEV_1) had to be ≥50% of the predicted values [19] and reversibility of FEV_1 had to be ≥15% in response to an inhaled β_2-agonist. The provocative dose of inhaled histamine causing a 20% fall in FEV_1 from pre-challenge values (PD_{20}histamine) was <0.59 µmol (<4 mg·ml^{-1}) for all subjects. None of the patients had used systemic corticosteroids for a period of six months or suffered from a respiratory tract infection for a period of one month before the start of the study. Twenty three patients used inhaled corticosteroids before entering the study with an average dose of 400 µg *b.i.d.* to control their asthma. All previous medication was stopped when the patients entered the first placebo period.

The study was approved by the local Ethics Committee and all patients gave their written informed consent.

Study design

The study was carried out according to a randomized, cross-over, double-dummy design (fig. 1). A three-week, single-blind, wash-out placebo period was followed by two periods of double-blind active treatment, each lasting eight weeks, and separated by a second single-blind, wash-out placebo period of three weeks. The placebo periods were regarded as the baseline before the active treatment periods.

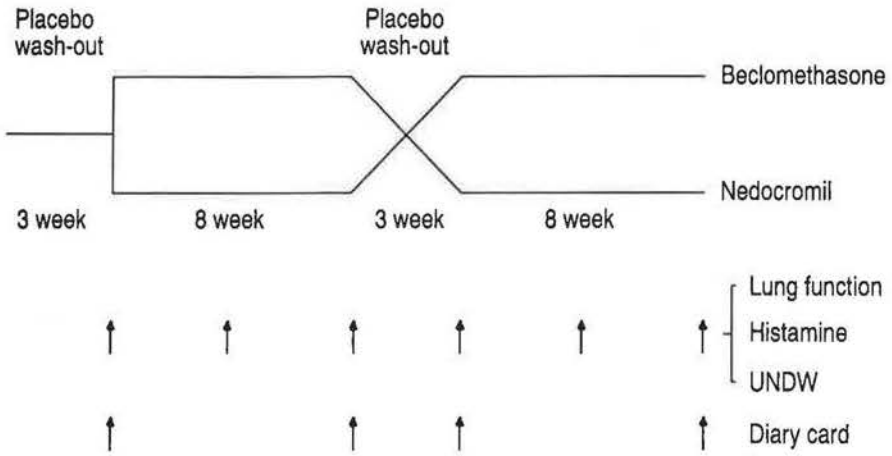

Fig. 1. – Study design of the double-blind, randomized, cross-over comparison of nedocromil sodium and beclomethasone in atopic asthmatic patients. UNDW: ultrasonically nebulized distilled water.

During the active treatment periods the patients inhaled nedocromil sodium, 4 mg *q.i.d.* (Fisons Ltd, Loughborough, UK) or beclomethasone dipropionate, 200 μg *q.i.d.* (Glaxo Ltd, The Netherlands) from a metered dose inhaler. During the study patients were allowed to inhale salbutamol from a metered dose inhaler as rescue medication. No other anti-asthma drugs were allowed during the trial.

Measurements

At the end of both placebo periods and after 4 and 8 weeks of active treatment, a histamine provocation test and an ultrasonically nebulized distilled water (UNDW) provocation test were performed on two different days with at least one day in between to avoid histamine-induced tachyphylaxis for UNDW-induced bronchoconstriction [20]. The variation in the pre-challenge FEV_1 on these two days had to be within 10%. Salbutamol was withheld for a period of at least 8 h before each test and the trial medication was stopped for a period of at least 24 h to avoid any direct drug effects on the provocation tests.

Lung function. Flow-volume curves were performed to measure lung function (Pneumoscreen II, Jaeger, Würzburg, FRG) before and during each provocation test. The mean of the FEV_1 values before the UNDW and histamine provocation tests in each period was regarded as the pre-challenge FEV_1.

Histamine provocation tests were performed according to RYAN *et al.* [21]. The patients inhaled doubling doses of histamine (0.03–16 $mg \cdot ml^{-1}$) from a dosimeter (Jaeger, Würzburg, FRG). Six maximal inspirations were used to deliver 45 μl of histamine per dose. Inhalation of 45 μl of a concentration of 1 $mg \cdot ml^{-1}$ resulted in a dose of 0.15 μmol. Flow-volume curves were recorded at 30, 90 and 180 s after inhalation. The PD_{20}histamine was calculated from baseline values by linear interpolation on a semi-logarithmic curve.

UNDW provocation tests were performed with the Ultraneb 99 ultrasonic nebulizer (DeVilbiss, Sommerset, USA), according to a modified method described by ANDERSON *et al.* [6]. The output was fixed at 2 $ml \cdot min^{-1}$ when the equipment was not attached. Air with UNDW was inhaled through a mouthpiece with tightened lips and nose clipped. A Leardal IV two-way valve (Stavanger, Norway), with a deadspace of 24 ml, was placed between the aerosol hose and the mouthpiece. A respirometer (British Oxygen Co., London, UK) was connected to the expiratory port of the two-way valve to measure the total volume of inhaled air. After inhalation of 20 *l* of ambient air through the system, doubling volumes of air with UNDW (3, 5, 10, 20, 40, 80 and 160 *l*) were inhaled at 5 min intervals. Flow-volume curves were recorded 30, 90 and 180 *s* after inhalation. The test was stopped when the last dose of air with UNDW, *i.e.* 160 *l*, was inhaled or a 20% fall in FEV_1 was achieved. Before and after each test the nebulizer chamber and aerosol hose were weighed and the total amount of inhaled UNDW was measured in $ml H_2O$. The provocative dose of inhaled distilled water in $ml H_2O$ causing a 20% fall in FEV_1 from post-air values (PD_{20}UNDW), was calculated by linear interpolation on a semi-logarithmic curve.

Diary card. Morning and evening peakflow measurements were recorded with a mini-Wright peakflow meter, the best of three attempts, and daily use of bronchodilators was registered as the total number of inhalations of salbutamol during the last two weeks of the placebo and the active treatment periods.

Statistical analysis

PD_{20}histamine and PD_{20}UNDW data, FEV_1 values and data obtained from diary cards were analysed by the Wilcoxon signed rank test. For multiple comparisons a Bonferroni correction was used. The shift in PD_{20} values was calculated as the difference between the real baseline values and the values after 4 and 8 weeks of treatment. The changes in PD_{20}

values were also expressed as doubling doses of inhaled histamine and UNDW, calculated from the individual baseline values. Period effects and carry-over effects were analysed according to Pocock [22] by the Mann-Whitney U-test. Correlations were calculated by the Spearman rank test. FEV_1 values are presented as percentage of predicted [19]. Data are presented as mean±standard error of mean (SEM) and statistical significance was accepted at $p<0.05$.

Results

The study was completed by 23 patients. Five patients (nos. 2, 10, 16, 17 and 28) were unable to come to the laboratory for lung function and provocation tests at the appointed intervals and withdrew from the study voluntarily during the first active treatment period. Patients nos. 2, 16, 17 and 28 had started with beclomethasone and no. 10 had started with nedocromil sodium. None of the patients failed to complete the study due to an exacerbation of their asthma or the need of additional medication. One patient (no. 23) did not react to UNDW. The diary cards of 18 patients could be evaluated for peakflow measurements and β_2-agonist use.

Of the 23 patients who completed the study, 11 patients started with beclomethasone and 12 with nedocromil sodium during the first active drug period. There were no period or carry-over effects for all parameters as shown in table 2.

None of the parameters, *i.e.* FEV_1, PD_{20}histamine, PD_{20}UNDW, β_2-agonist use and peakflow measurements were significantly different in the two baseline periods (table 3). Treatment with beclomethasone induced a significant improvement of the mean FEV_1 and decreased bronchial hyperresponsiveness to histamine and UNDW (table 2 and fig. 2) after 4 and 8 weeks of treatment as compared to the baseline values. Nedocromil sodium decreased bronchial hyperresponsiveness to histamine, but not to UNDW after 4 and 8 weeks of treatment and did not improve FEV_1 as compared to the baseline values during placebo treatment. Treatment with beclomethasone was significantly better for all parameters, except for the FEV_1 after 4 weeks of treatment.

The changes in PD_{20}histamine and PD_{20}UNDW, expressed as doubling doses, are presented in table 4. There was no significant difference in doubling doses between histamine and distilled water.

Table 2. – Carry-over and period effects of the two active treatment periods

	Group I* (n=11)	Group II** (n=12)	Carry-over effect	Period effect
PD_{20}histamine µmol				
Beclomethasone				
Baseline	0.02	0.07		
8 weeks	0.30	0.44		
Nedocromil				
Baseline	0.03	0.06		
8 weeks	0.12	0.15	p=0.49	p=0.67
PD_{20}UNDW mlH_2O				
Beclomethasone				
Baseline	0.9	1.7		
8 weeks	4.1	6.4		
Nedocromil				
Baseline	1.7	2.0		
8 weeks	1.8	1.0	p=0.38	p=0.32
FEV_1 %pred				
Beclomethasone				
Baseline	79	81		
8 weeks	91	89		
Nedocromil				
Baseline	82	82		
8 weeks	86	85	p=0.36	p=0.81
β_2-agonist use puffs·day^{-1}	(n=8)	(n=10)		
Beclomethasone				
Baseline	2.3	5.5		
8 weeks	2.0	2.5		
Nedocromil				
Baseline	3.6	3.2		
8 weeks	5.5	4.5	p=0.29	p=0.15

*: Group I represents the patients who started with beclomethasone; **: Group II represents the patients who started with nedocromil sodium. The data are expressed as geometric means. For abbreviations see legend to table 1.

Table 3. – FEV_1 and PD_{20} values, peakflow rate in the morning and the evening, and β_2-agonist use during baseline and after 4 and 8 weeks of treatment

		Baseline	4 week treatment	8 week treatment
Beclomethasone				
FEV_1	% pred	79.8±3.7	89.6±3.4**	89.5±3.0†
PD_{20}histamine	µmol	0.04±0.03	0.28±0.13***††	0.37±0.18***†††
PD_{20}UNDW	mlH_2O	1.3±0.6	5.3±2.2	6.2±2.5***††
Peakflow	$l \cdot min^{-1}$			
Morning		459±23		494±26*†
Evening		470±22		505±25*†
β_2-agonist use	puffs·day^{-1}	3.3±0.8		2.2±0.5**††
Nedocromil sodium				
FEV_1	% pred	82.4±3.7	86.4±3.0	84.8±3.3
PD_{20}histamine	µmol	0.05±0.04	0.10±0.03**	0.13±0.07***
PD_{20}UNDW	mlH_2O	1.9±0.7	2.7±1.5	1.8±2.0
Peakflow	$l \cdot min^{-1}$			
Morning		468±24		471±23
Evening		489±22		492±23
β_2-agonist use	puffs·day^{-1}	3.4±0.8		4.9±0.8

Data are presented as geometric mean±SEM; *: p<0.05; **: p<0.005; ***: p<0.0005 *versus* the baseline; †: p<0.05; ††: p<0.005; †††: p<0.0005 *versus* nedocromil sodium. For abbreviations see legend to table 1.

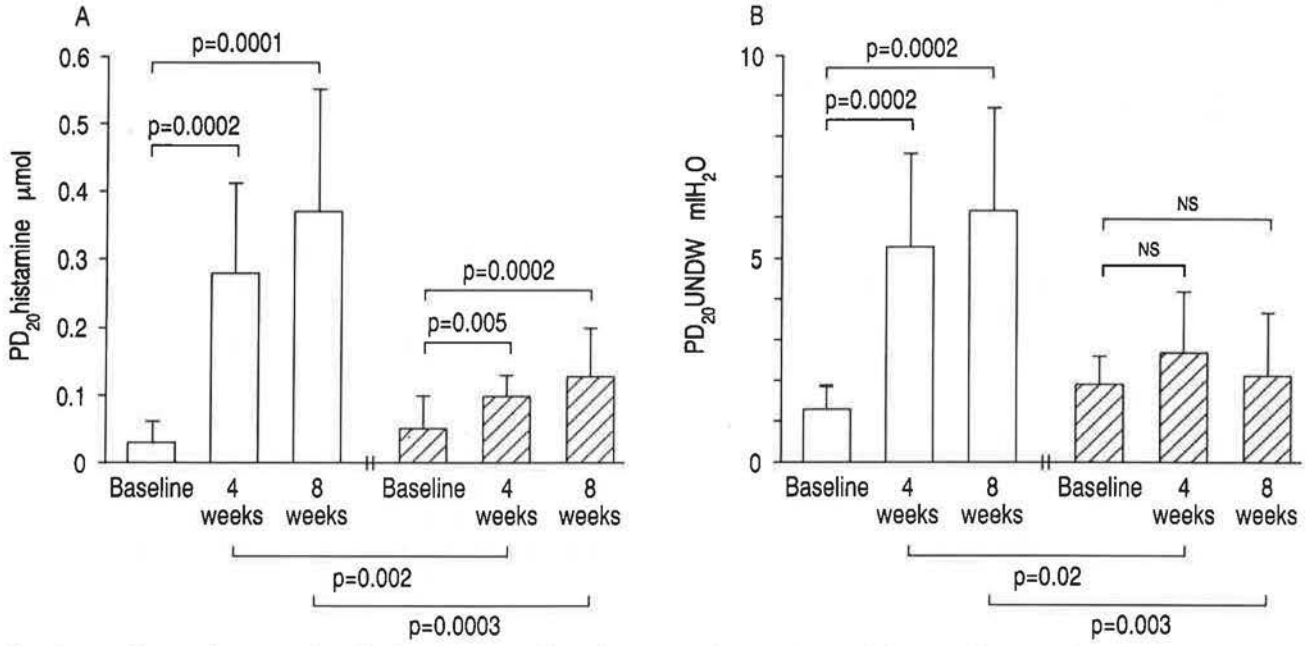

Fig. 2. – Geometric means (±SEM) of: A) the PD_{20}histamine; and B) PD_{20}UNDW during baseline and after 4 and 8 weeks of treatment with beclomethasone ☐ and nedocromil sodium ▨. PD_{20}: provocative dose producing a 20% fall in forced expiratory volume in one second from baseline; UNDW: ultrasonically nebulized distilled water.

Table 4. – Changes in PD_{20}histamine and PD_{20}UNDW calculated from baseline values and expressed as doubling doses

	4 week treatment	8 week treatment
Beclomethasone		
PD_{20}histamine	2.5±0.4*	2.9±0.4*
PD_{20}UNDW	1.8±0.3**	2.3±0.4**
Nedocromil sodium		
PD_{20}histamine	1.2±0.3	1.4±0.3
PD_{20}UNDW	0.7±0.2	0.8±0.3

Data are presented as mean±SEM. *: p<0.05; **: p<0.01 *versus* nedocromil sodium. For abbreviations see legend to table 1.

A significant correlation was found between PD_{20}histamine and PD_{20}UNDW during placebo (r_s=0.76) and after 8 weeks of treatment with beclomethasone (r_s=0.73) and nedocromil sodium (r_s=0.87) ($p<0.005$ for the three periods). The shift in PD_{20}histamine and PD_{20}UNDW after 4 weeks of treatment with beclomethasone showed no correlation, whereas after 8 weeks of treatment a significant correlation (r_s=0.64, p=0.004) was found. There were no correlations between the PD_{20} values for histamine and UNDW and the pre-challenge FEV_1.

Both morning and evening peakflow rates were significantly increased and β_2-agonist use was significantly decreased after 8 weeks of treatment with beclomethasone compared to the baseline values and treatment with nedocromil sodium (table 3 and fig. 3).

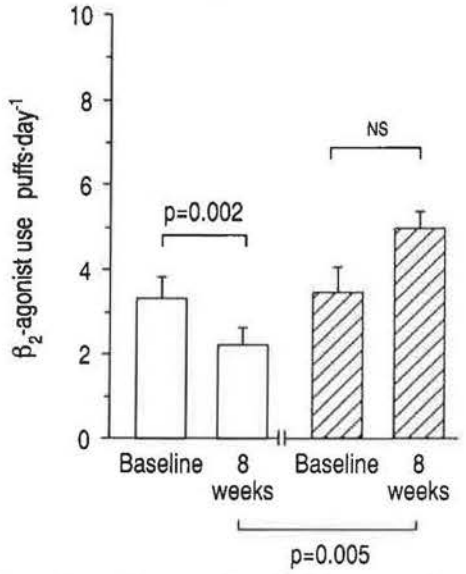

Fig. 3. – Geometric means (±SEM) of the β_2-agonist use during the last week of the baseline period and beclomethasone ☐ and nedocromil sodium treatment ▨.

Discussion

The results of our study demonstrate that, in patients with allergic asthma, treatment with inhaled beclomethasone, in a total daily dose of 800 μg, improves lung function and decreases bronchial hyperresponsiveness to histamine and distilled water provocation, after 4 and 8 weeks of treatment. Beclomethasone also reduces the need for additional bronchodilators as reflected by a decrease in daily use of salbutamol. Nedocromil sodium, with a total daily dose of 16 mg, decreases bronchial hyperresponsiveness to histamine, but not to UNDW, after 4 and 8 weeks of treatment. Nedocromil sodium had no effect on lung function or β_2-agonist use. Bronchial hyperresponsiveness and most lung function parameters were significantly better during treatment with beclomethasone than with nedocromil sodium.

Our results are partly comparable with those of a study in non-allergic patients with mild asthma [23], comparing a total daily dose of 400 μg beclomethasone with 16 mg nedocromil sodium. The authors measured a significant decrease in bronchial hyperresponsiveness to methacholine after 4 and 8 weeks of treatment with beclomethasone, and after 8 weeks of treatment with nedocromil sodium. Only beclomethasone could induce a significant increase in lung function, but no significant differences were found between beclomethasone and nedocromil sodium [23].

In the present study, beclomethasone induced a significant increase in both morning and evening peakflow rates, whereas nedocromil sodium had no significant effects. These findings are in contrast with those of a study comparing beclomethasone, 400 μg daily, with nedocromil sodium, 16 mg daily, in a group of 13 asthmatic subjects [24]. This study showed that after 8 weeks of treatment with both beclomethasone and nedocromil sodium there were significant increases in morning and evening peakflow rates. β_2-agonist use was lower during beclomethasone treatment, whereas nedocromil sodium had no significant effect.

The significantly better effect of beclomethasone, compared to nedocromil sodium, on bronchial hyperresponsiveness, lung function and β_2-agonist use in our group of atopic asthmatic patients is probably related to the dose of beclomethasone used and the characteristics of our patients with respect to their degree of airway hyperresponsiveness. Other studies [23–25], investigating a lower dose of beclomethasone, *i.e.* 400 μg daily, and an equal amount of nedocromil sodium, *i.e.* 16 mg, did not demonstrate significant differences between treatments. A further difference between these studies [23–25] and ours is the degree of bronchial hyperresponsiveness. Twenty three of our patients used inhaled corticosteroids before entering the study, in contrast to a minority of the patients from the other studies [23–25]. This may indicate more severe asthma in our group of patients. Nevertheless, nedocromil sodium in a total daily dose of 16 mg seems to be less potent in this group of patients. Comparing the duration of treatment needed to achieve significant effects on asthma, beclomethasone-induced changes can be demonstrated after 3–4 weeks of treatment, whereas the effects of nedocromil treatment become clear after 4–8 weeks of treatment, as can be concluded from our data and the data from the other studies [23–25]. During beclomethasone treatment the bronchial hyperresponsiveness to histamine further improved between 4–8 weeks of treatment, whereas this effect could not be demonstrated for nedocromil sodium.

Beclomethasone treatment significantly improved both FEV_1 and bronchial hyperresponsiveness to histamine and UNDW. This may suggest that the improvement in bronchial hyperresponsiveness is partly the result of increase in lung function. Although a correlation between the degree of airway obstruction and bronchial hyperresponsiveness has been found in a heterogeneous population [26], this correlation does not seem to exist in asthmatic subjects, in contrast to patients with a chronic airway obstruction [27].

For asthmatics, this is confirmed by our data, since we also could not demonstrate a correlation between the pre-challenge FEV_1 and the PD_{20}histamine or PD_{20}UNDW. Hence, in asthma the pre-challenge FEV_1 seems to be a relatively minor determinant for the improvement of bronchial hyperresponsiveness.

PD_{20}histamine and PD_{20}UNDW showed a good correlation during the trial. The shifts in PD_{20} values for histamine and UNDW were not significantly different. Therefore, it appears that histamine and UNDW are equally sensitive in detecting changes in bronchial hyperresponsiveness induced by anti-inflammatory drugs, such as beclomethasone, in asthmatic patients. However, during beclomethasone treatment there was no correlation between the change in PD_{20}histamine and PD_{20}UNDW after 4 weeks of treatment, whereas after 8 weeks of treatment a significant correlation was found. Furthermore, the increase in PD_{20}histamine was significantly more pronounced after 8 weeks of treatment with beclomethasone than after 4 weeks. This indicates that beclomethasone-induced effects in asthma are probably measured by histamine and UNDW challenge on a different level of bronchial responsiveness. These findings are supported by our knowledge of the underlying mechanisms in histamine- and UNDW-induced bronchoconstriction, which are not identical. The histamine bronchoconstrictor response is mainly a direct effect of the drug on the airway smooth muscles [7], whereas in UNDW-induced bronchoconstriction the release of mediators from inflammatory cells, such as mast cells, seems also to be involved [28]. Pre-inhalation of sodium cromoglycate can totally block UNDW-induced bronchoconstriction and prevent mediator release [6, 29], but it has no effect on histamine-induced bronchoconstriction [30].

Nedocromil sodium also has an inhibitory effect on UNDW-induced bronchoconstriction when inhaled 30 min before the challenge [14, 31]. The duration of this protective effect in UNDW provocation is unknown. In exercise testing the protective effect of nedocromil sodium lasts at least 2 h [17]. We arbitrarily stopped beclomethasone and nedocromil sodium for a period of 24 h before histamine and UNDW challenge to prevent a direct blocking effect on the bronchoprovocation tests. The lack of a significant change in PD_{20}UNDW during nedocromil sodium indicates that after 24 h the direct inhibitory effect, probably caused by a blockade of mediator release, has disappeared. The beneficial effect of beclomethasone was not influenced by the 24 h withdrawal period. In contrast to the inhaled corticosteroids, nedocromil sodium in this dose appears to have no long-lasting effects on mediator release, as measured by UNDW-induced bronchoconstriction. The sole effect of nedocromil sodium treatment in our study was a decrease in bronchial hyperresponsiveness to histamine. The mode of action of long-term effects of nedocromil sodium in asthmatic subjects is not known. This decrease in bronchial hyperresponsiveness to histamine probably indicates a reduction of the inflammation in the airway smooth muscles, although treatment with nedocromil sodium could not improve the other parameters.

Topically administered corticosteroids have been shown to reduce the number of mast cells in the skin and diminish the measurable histamine release dramatically [32]. In asthmatics, corticosteroid treatment induces a significant fall in whole blood histamine, a mast cell mediator [33]. Thus, corticosteroids appear to deplete or reduce the stores of histamine in tissue [34, 35] and probably modify mediator release [35]. This may partly explain the difference in treatment effects of both drugs on UNDW-induced bronchoconstriction.

We conclude that nedocromil sodium, 16 mg daily, has anti-asthmatic properties in this group of allergic asthmatic patients, as demonstrated by a significant decrease in bronchial hyperresponsiveness to histamine after 4 and 8 weeks of treatment. However, beclomethasone, 800 μg daily, showed superior effects compared to nedocromil sodium with regard to the decrease in β_2-agonist use after 8 weeks of treatment, the increase in lung function after 4 and 8 weeks and the decrease of bronchial hyperresponsiveness measured by histamine and UNDW after 4 and 8 weeks of treatment.

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