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Nedocromil sodium in obstructive airways disease: effect on symptoms and plasma protein leakage in sputum

D.F.M. Schoonbrood*†, T.A. Out†+, A.A.M. Hart++, F.J.M. Habets*†, C.M. Roos*, H.M. Jansen*

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ABSTRACT: In patients with asthma or chronic obstructive pulmonary disease, there is chronic airway inflammation with increased leakage of plasma proteins into the airway lumen, which can be reduced by inhaled glucocorticosteroids. Nedocromil sodium is an anti-inflammatory drug, and we questioned whether it also affects the leakage of plasma proteins.

In a double-blind placebo-controlled study we investigated the effect of 12 weeks of treatment with nedocromil on forced expiratory volume in one second (FEV_1), provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}), peak flow, symptom scores, and plasma protein leakage in sputum, in 31 patients with obstructive airways disease and sputum production (mean (range) FEV_1 61% of predicted (42–87%); geometric mean (range) PC_{20} 0.39 (0.04–2.9) $mg \cdot mL^{-1}$). As a measure for plasma protein leakage we calculated the relative coefficients of excretion (RCE) of proteins from serum to the soluble phase of sputum.

There was a small increase in morning and evening peak flow ($p<0.05$) and a decrease in night-time bronchodilator use ($p<0.02$) in favour of nedocromil. The RCE of α_2-macroglobulin to albumin significantly decreased after treatment with nedocromil ($p=0.03$).

The results show limited clinical efficacy of nedocromil in our study group. They further suggest that the anti-inflammatory properties of nedocromil extend to inhibition of plasma protein leakage into the airways.

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*Dept of Pulmonology, †Clinical and Laboratory Immunology Unit, and ++Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam. +Laboratory for Experimental and Clinical Immunology, CLB, Amsterdam, The Netherlands.

Correspondence: H.M. Jansen, Academic Medical Center, University of Amsterdam, Dept of Pulmonology, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands

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In patients with bronchial asthma or chronic obstructive pulmonary disease (COPD), there is chronic inflammation of the airway mucosa [1]. Features of this process are abnormal local secretion of proteins [2], and an increased permeability of the airway microvasculature and epithelium, resulting in extravasation of plasma proteins into the bronchial lumen [1, 3]. In support of this, high levels of plasma proteins were demonstrated in sputum from patients with asthma or COPD [4], which, in asthma, was correlated with bronchial hyperreactivity [5]. Protein leakage into sputum was reduced after treatment with glucocorticosteroids [4, 6, 7]. The effects of glucocorticosteroids were confirmed by our study in bronchoalveolar lavage fluid (BALF) [8] and sputum [9].

Little is known about the effect of other classes of anti-asthma drugs on plasma protein leakage. One study confirmed that the raised albumin content in sputum from patients with asthma returned to control values after 2 days of treatment with cromolyn sodium [10]. Nedocromil sodium induced a decrease of inflammatory cells and mediators in the BALF and reduced the plasma protein leakage into lung epithelial lining fluid [11–13]. No data are available on its possible effect on plasma exudation in sputum.

As shown in a previous feasibility study, sputum analysis is a reliable method to obtain information on the local inflammatory process in the airways in patients with obstructive airways disease [5]. Here we report a double-blind placebo-controlled study with nedocromil sodium in obstructive airways disease. Regular assessments were made of proteins in sputum and the extent to which any changes correlated with changes in bronchial hyperresponsiveness and the number of eosinophils in the blood.

Patients and methods

Patients

The study protocol was approved by the Medical Ethics Committee of our hospital, and written informed consent was obtained from the patients.

Patients were selected from the out-patient pulmonology clinic according to the following inclusion criteria: 1) a forced expiratory volume in one second (FEV_1) <80% of predicted, within the previous 6 months; 2) airway responsiveness to histamine aerosol (provocative

concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) <16 $mg \cdot mL^{-1}$); 3) sputum production on a regular basis; 4) ability to use pressurized aerosol and peak flow meter correctly; 5) ability to keep a daily diary card; and 6) no other major illnesses. An additional inclusion criterion at the end of the baseline period was a total score of ≥10 for at least one symptom during at least 7 days of the baseline period as recorded on the diary card. Exclusion criteria at entry were: 1) pregnancy, risk of pregnancy or breast-feeding; 2) significant renal, hepatic or cardiovascular disease; and 3) FEV_1 <40% pred normal. None of the patients had experienced an airway infection or exacerbation within 3 weeks of start of the study. Inhaled corticosteroids and cromolyn sodium were stopped 6 weeks before the onset of the baseline period. The permitted medication is shown in table 1.

The patients that participated in the study are described in table 1. They had moderately severe obstructive airways disease (mean (range) FEV_1, 61% pred (41–87%)), with a mean (range) bronchodilator response to terbutaline of 13% (0–53%) of baseline FEV_1. They were classified retrospectively as asthma or COPD patients according to the American Thoracic Society (ATS) criteria [14].

Study design

The present study had a double-blind placebo-controlled group comparative design. A 2 week baseline period was followed by a 12 week treatment period. At the end of the baseline period, at Visit two, patients were randomized to receive either nedocromil sodium (4 mg *q.i.d.*), or matching placebo. Visits were made to the

Table 1. – Baseline characteristics of patients

Ss				Visit 1		Visit 2				
No.	Sex	Age yrs	Diagnosis	PC_{20} $mg \cdot mL^{-1}$	PBEos $10^6 \cdot L^{-1}$	FEV_1 pre % pred	FEV_1 post % pred	Atopy*	Smoking	Medication
Nedocromil										
1	M	63	COPD	1.28	370	52	58	-	ex	IB, IP
2	F	66	COPD	0.11	260	42	45	+	+	IB, IP, TH
3	M	60	COPD	0.85	270	49	47	-	+	IB, IP, TH
4	M	54	Asthma	0.65	180	51	60	+	-	AC
5	F	43	COPD	0.39	80	86	93	+	-	IB, TH
6	F	53	COPD	0.82	150	61	67	-	+	IP
7	M	56	COPD	0.40	130	57	66	-	+	IB, AC
8	M	53	Asthma	0.99	130	59	64	-	+	IB
9	M	43	Asthma	1.20	220	83	87	-	+	IB, OB
10	M	64	COPD	0.09	30	41	47	-	+	IB
11	F	48	COPD	2.06	170	48	55	-	+	IB, AC
12	F	65	COPD	0.06	100	66	72	-	+	IB
13	M	70	COPD	0.81	160	68	77	+	+	IB
14	F	28	Asthma	0.19	310	62	66	+	-	IB, IP, AC
15	F	67	Asthma	0.34	90	82	91	-	+	IB
Mean		55.5†		0.45‡	151‡	60.4	66.2			
SEM		2.3				3.7	3.5			
Placebo										
16	M	53	COPD	2.92	80	80	82	-	+	IP
17	M	66	Asthma	0.27	330	46	49	+	-	IB
18	F	47	Asthma	0.04	650	63	93	-	-	IB, OB, IP
19	F	53	Asthma	0.29	130	58	66	+	+	IB, OB
20	M	34	Asthma	0.19	210	44	67	+	-	IB
21	M	59	Unclassifiable	1.08	220	77	77	+	+	IB, TH
22	M	41	Asthma	0.41	60	61	79	+	+	IB
23	M	41	Asthma	0.04	300	62	71	+	+	IB
24	M	43	Asthma	1.67	60	83	92	-	+	IB, OB
25	M	49	Asthma	0.23	510	58	67	-	+	IB, IP
26	M	58	Asthma	1.36	380	87	95	-	-	IB
27	F	49	Asthma	0.18	150	66	73	-	-	IB
28	M	34	Asthma	0.17	340	47	54	-	+	IB
29	F	52	COPD	0.14	190	48	54	+	+	IB
30	M	37	Asthma	0.25	1000	61	66	+	-	IB
31	M	42	Asthma	1.24	50	56	62	-	+	IB, IP
Mean		47.4		0.33‡	209‡	62.3	71.7			
SEM		3.0				3.4	4.0			

Ss: subjects; PC_{20}: provocative concentration of histamine causing a 20% fall in forced expiratory volume in one second (FEV_1); PBEos: eosinophil count in peripheral blood; M: male; F: female; COPD: chronic obstructive pulmonary disease; - : no; + : yes; IB: inhaled β-agonist; OB: oral β-agonist; IP: ipratropium bromide; TH: theophylline; AC: acetylcysteine; pre: prebronchodilator; post: postbronchodilator; ex: ex-smoker. *: positive radioallergosorbent test or skin-prick test to one or more inhalant allergens. †: significantly different compared to placebo (unpaired t-test, p=0.04). ‡: geometric mean.

clinic for lung function tests, sputum delivery, and a review by the investigator at the beginning and the end of the baseline (Visit one and two, respectively), and at 4, 8 and 12 weeks of treatment. At the end of the first treatment week, the investigator visited the patients at home for an extra review, and to obtain a sputum and a blood sample.

At the beginning of the baseline period, and after 12 weeks of treatment, a histamine provocation test was performed. The bronchial reactivity to histamine was determined with a 2 min tidal breathing method [5, 15]. At the end of the baseline period and after 4, 8 and 12 weeks of treatment the bronchodilator response was assessed by measuring FEV_1 [5, 16] before and 20 min after inhalation of four puffs of 250 µg of terbutaline sulphate administered through a spacer device. For each patient the lung function tests were performed at the same time of day. Inhaled bronchodilators and the study drug were stopped 8 h, and oral bronchodilators 24 h, before the lung function test.

During the whole study period the patients recorded on the diary card: night-time symptoms; wheeze breathlessness; cough; sputum; number of actuations of inhaled bronchodilators during night-time and daytime; the number of actuations of inhaled study drug; concomitant medication; and morning and evening peak expiratory flow (PEF). PEF was measured with a mini-Wright peak flow meter, at least 4 h after inhaling a bronchodilator, and the best of three attempts was recorded on the diary card. Diary cards and the technique of inhaling were checked at each visit. To check compliance in taking nedocromil sodium or placebo the drug canisters were weighed at each visit by an independent laboratory assistant. At the end of baseline, and after 4, 8 and 12 weeks of treatment the investigator scored the severity of the airways disease in the previous 2 weeks.

At each visit a 24 h sputum sample was collected, and a blood sample was taken to obtain serum and ethylenediamine tetraacetic acid (EDTA) plasma. EDTA plasma was used for blood eosinophil counts. Serum was stored at -80°C before protein analysis.

Sputum collection and analysis

The patients collected sputum at home over a 24 h period. Selection of proteins to be measured in the sputum sol phase (SSP) was based primarily on the relative molecular mass (M_r) and their origin. Proteins such as albumin (Alb), ceruloplasmin (CP) and α_2-macro-globulin (α_2-m) are thought to enter the airway lumen mainly by diffusion from the blood. Lactoferrin and serum immunoglobulin A (sIgA) are proteins that are produced locally and are supposed to be markers of airway secretion. The proteins were measured as described earlier [5, 17, 18]. To correct for their serum levels, the proteins albumin, ceruloplasmin and α_2-m in sputum were expressed as the concentration ratio ($Q_{protein}$): (10^3 × concentration of specific protein in sputum)/(concentration of specific protein in serum). The relative coefficient of excretion (RCE) of proteins from serum to SSP was determined [19, 20] according to:

$$RCE = Q\alpha_2\text{-m}/Q_{alb}$$
$$\text{and } RCE = Q\alpha_2\text{-m}/Q_{cp}$$

where $Q\alpha_2$-m, Q_{alb}, and Q_{cp} are the $Q_{protein}$ values for α_2-m, alb and cp, respectively. With these RCE values we corrected for the dilution effects. In addition, RCEs may be considered sensitive parameters for variations in the permeability of the respiratory membrane as diffusion of a high molecular mass protein, such as α_2-m, across the respiratory membrane is compared with that of smaller ones like albumin and ceruloplasmin [20], thereby recording the loss of size selectivity of the respiratory membrane that occurs during inflammation.

Statistical analysis

Mean diary card symptoms, inhaled bronchodilator use, and evening and morning PEF were calculated for the 2 weeks baseline, and for the treatment periods week 1–4, week 5–8 and week 9–12. For treatment failures, the mean of the last 3 days before stopping test treatment was calculated for all efficacy variables on the diary cards, and carried forward for the remainder of the treatment period. The PC_{20}, blood eosinophil counts and sputum protein data were logarithmically transformed before statistical analysis. Baseline (prerandomization) differences between the treatment groups were analysed using the Student's t-test for group means or Mann-Whitney U-test, as appropriate. Postrandomization, changes from baseline in diary card variables were analysed with the Mann-Whitney U-test. The p-values were corrected for multiple comparisons using the Hommel procedure [21]. Differences in lung function parameters, PC_{20}, blood eosinophil counts and sputum data were analysed using repeated measurement analysis of variance with treatment as a factor and (the mean of) the prerandomization measurement(s) as covariate. Patients with one or more missing values were retained in this analysis by using maximum likelihood methods.

The effect of the diagnosis of asthma and COPD on the influence of nedocromil sodium on lung function parameters, PC_{20}, blood eosinophil counts and sputum data was analysed in a similar manner in a retrospective study, comparing the differences between nedocromil sodium and placebo in asthma patients with those in COPD patients (diagnosis×treatment interaction).

Spearman rank correlation coefficients (r) were calculated for RCE and PC_{20} and for RCE and blood eosinophil counts. A p-value of less than 0.05 was considered statistically significant.

Results

Sixty four patients agreed to participate in the study; 23 dropped out before entering the baseline period. Of the 41 patients that entered the baseline period, 10 did not fulfil the inclusion criteria at the end of the baseline period, because of a total symptom score of <10 (n=6), purulent sputum (n=2), noncompliance (n=1), or an FEV_1 <40% pred (n=1). Thirty one patients were randomized to receive nedocromil sodium (n=15) or placebo (n=16) (tables 1 and 2). Twenty five patients completed the study; six were withdrawn (five treatment failures (four placebo, one nedocromil) and one loss of compliance). Sputum data from one patient in the placebo group were excluded because in three out of seven

Table 2. – Baseline and changes from baseline in lung function, PC_{20}, and blood eosinophil count during nedocromil sodium and placebo treatment

		Baseline n=31	4 weeks n=28	8 weeks n=26	12 weeks n=25
FEV_1 prebronchodilator L	N	1.84 (0.15)	0.04 (0.05)	-0.02 (0.08)	-0.02 (0.11)
	P	2.21 (0.16)	-0.12 (0.09)	-0.117 (0.06)	-0.18 (0.11)
FEV1 postbronchodilator L	N	2.01 (0.15)*	0.03 (0.05)	0.02 (0.06)	0.12 (0.08)
	P	2.54 (0.17)	-0.20 (0.08)	-0.18 (0.07)	-0.20 (0.11)
Morning PEF $L \cdot min^{-1}$	N	290.9 (19.7)	16.2 (6.6)	22.01 (9.7)	25.7 (10.5)*
	P	352.6 (22.6)	-2.3 (6.5)	-1.1 (9.8)	-8.4 (8.7)
Evening PEF $L \cdot min^{-1}$	N	296.0 (20.2)*	10.0 (5.1)	19.1 (8.7)	20.8 (10.0)*
	P	376.0 (23.7)	-0.8 (6.6)	-17.6 (10.9)	-9.1 (8.2)
PC_{20} log	N	-0.34 (0.12)			-0.13 (0.13)
	P	-0.48 (0.14)			0.15 (0.14)
Eosinophils log	N	2.18 (0.07)	-0.01 (0.04)		-0.03 (0.02)
	P	2.31 (0.10)	0.06 (0.03)		-0.03 (0.06)
SSF %	N	62.2 (4.2)	-3.85 (1.65)	-2.95 (3.02)	2.42 (2.98)
	P	62.9 (6.2)	5.3 (2.93)	3.0 (2.78)	2.69 (3.77)

Values are presented as mean, and SEM in parenthesis. N: nedocromil sodium; P: placebo; PEF: peak expiratory flow; SSF: sputum sol fraction. *: significantly different compared to placebo: unpaired t-test; $p<0.05$.

samples his sputum protein levels were below the detection limit.

Generally, compliance with test medication was good, as checked from the diary card records and the canister weights. No serious adverse events were reported in the nedocromil or in the placebo group. Seven patients (four nedocromil, three placebo) received antibiotics during the treatment period (all in the period 4–12 weeks) because of episodes of upper respiratory tract infection. The data from these patients were included in the analysis.

Effect of nedocromil sodium on clinical variables

There was no increase in FEV_1 prebronchodilator after treatment with nedocromil sodium (p=0.76; table 2). The FEV_1 postbronchodilator increased by 0.12 L after 12 weeks of nedocromil treatment and decreased by 0.20 L after placebo treatment (p=0.06; table 2). The morning PEF and evening PEF increased after 12 weeks treatment with nedocromil by 25.7 and 20.8 $L \cdot min^{-1}$, respectively, and decreased by 8.4 and 9.1 $L \cdot min^{-1}$, respectively, after placebo treatment (p=0.04; table 2). For the evening PEF there was also a difference in change over time, in favour of nedocromil (p=0.013). The mean night-time bronchodilator use decreased from 1.28 to 0.69 inhalations after treatment with nedocromil and increased after treatment with placebo from 1.34 to 1.75 inhalations. This difference was statistically significant after 12 weeks (p=0.015; fig. 1). There were no significant differences in change from baseline for the PC_{20}, blood eosinophil counts (table 2), in day-time bronchodilator use, symptom scores and severity of airways disease as scored by the investigator.

In addition, in a retrospective study, we analysed the influence of clinical diagnosis on the effects of nedocromil sodium. There was a tendency for the diagnosis to influence the effect of nedocromil sodium on FEV_1 postbronchodilator (p=0.063). There was no statistically significant influence of the diagnosis on the effect of treatment on morning or evening PEF, and no effect on night-time bronchodilator use.

Effect of nedocromil sodium on sputum proteins

There was no significant difference between the two treatment groups in baseline 24 h sputum weight (mean± SEM sputum weight: nedocromil 14.3±3.7 g, placebo 8.1± 1.7 g) and sputum sol fraction (percentage of total sputum weight; table 2). The two groups did not differ with respect to baseline Q_{alb}, Q_{cp}, or $Q\alpha_2$-m, and levels of lactoferrin and sIgA in SSP. Sputum volume did not change after treatment with nedocromil sodium or placebo. The sputum sol fraction showed an average decrease of 8% in the nedocromil group after 4 weeks and a 9% increase in the placebo group (table 2), but this difference was not statistically significant. When only the patients without missing values were analysed, the difference became significant (p=0.045). No significant effect of nedocromil was seen for the Q_{alb}, Q_{cp} and $Q\alpha_2$-m, or for lactoferrin and sIgA.

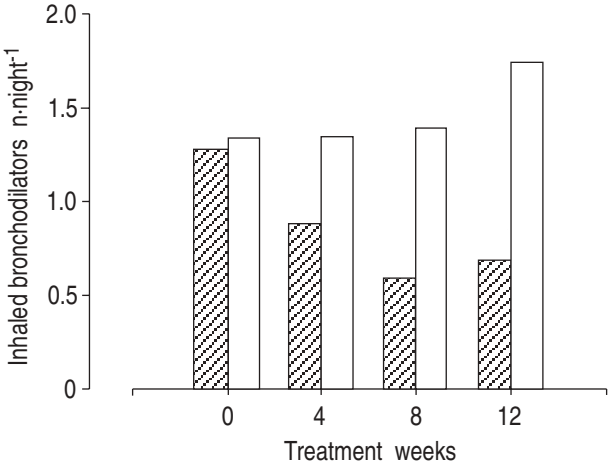

Fig. 1. – Mean number of inhaled bronchodilators used at night during a 12 week treatment with nedocromil sodium (▭) or placebo (▭). Change from baseline was significantly different between the two treatment groups after 12 weeks: Mann-Whitney U-test, p=0.015.

There was no difference in baseline RCE $Q\alpha_2$-m/Q_{alb}, nor for the RCE $Q\alpha_2$-m/Q_{cp}. After treatment with nedocromil there was a significant decrease in the $Q\alpha_2$-m/Q_{alb}, (overall difference between treatments: p=0.03; fig. 2), with the maximal decrease being 25% after 4 weeks. For the RCE $Q\alpha_2$-m/Q_{cp}, a similar decrease was seen after 4 weeks of treatment with nedocromil, but this was not significantly different from placebo. The correlations between the $Q\alpha_2$-m/Q_{cp} and $Q\alpha_2$-m/Q_{alb}, and

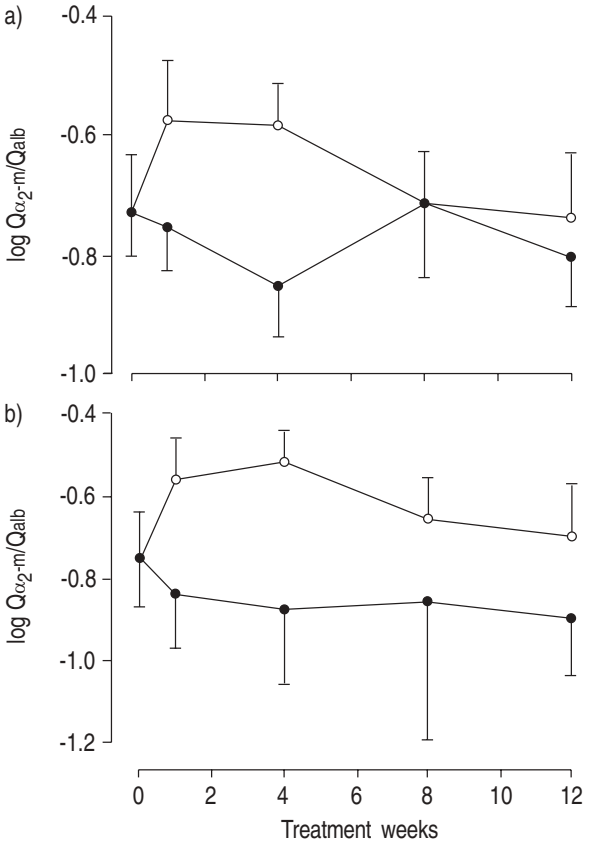

Fig. 2. – Mean (±SEM) log $Q\alpha_2$-m/Qalb for: a) all patients; and b) asthma patients, during a 12 week treatment with nedocromil sodium (●) or placebo (○). Data at week 0 are the mean of value at Visit 1 and Visit 2. Overall postrandomization difference was significantly different between nedocromil and placebo treatment: a) all patients, p=0.03; b) asthma patients, nedocromil (n=5), placebo (n=13), p<0.01. $Q\alpha_2$-m: concentration ratio of α_2-macroglobulin; Qalb: concentration ratio of albumin.

the number of eosinophils in the peripheral blood are shown in table 3. In addition, a significant correlation was observed between the change in $Q\alpha_2$-m/Qcp and the change in the number of blood eosinophils (after 4 weeks: r=0.48, p=0.01; and after 12 weeks: r=0.43, p=0.03).

The retrospective analysis of COPD and asthma as separate groups revealed that in asthma, nedocromil sodium had a significant effect on the $Q\alpha_2$-m/Qalb and $Q\alpha_2$-m/Qcp (overall difference between nedocromil sodium and placebo: p<0.01 (fig. 2) and p<0.04, respectively). For other sputum parameters, no effects of diagnosis were found.

In addition, it was found that in the asthma patients, the RCE $Q\alpha_2$-m/Qcp and $Q\alpha_2$-m/Qalb were significantly correlated with blood eosinophils at baseline (r=0.72 and 0.51, respectively; p<0.01 and p=0.04, respectively), and after 4 weeks treatment (r=0.68 and 0.50, respectively; p<0.01 and p=0.054, respectively). There was a significant correlation between the change from baseline of $Q\alpha_2$-m/Qcp after 12 weeks with that of blood eosinophils (r=0.73, p<0.01). The correlation between changes from baseline of $Q\alpha_2$-m/Qalb and those of eosinophils was: r=0.50 (p=0.054). In the asthma patients there was a significant correlation between $Q\alpha_2$-m/Qalb and PC20 at baseline (r=-0.53, p=0.028). Changes in the RCE were not significantly correlated with those in PC20.

Table 3. – Spearman rank correlation coefficients (r) for relationship between relative coefficient of excretion (RCE) and blood eosinophil count at baseline (Visit 1) and during treatment

		$Q\alpha_2$-m/Qcp		$Q\alpha_2$-m/Qalb	
	n	r	p-value	r	p-value
Baseline	30	0.69	0.001	0.49	0.006
Week 4	28	0.57	0.001	0.43	0.02
Week 12	27	0.44	0.02	0.33	0.09

$Q\alpha_2$-m, Qcp, Qalb: concentration ratios of α_2-macroglobulin (α_2-m), ceruloplasmin (cp) and albumin (alb), respectively.

Discussion

The effect of nedocromil sodium was investigated in patients with moderately severe obstructive airways disease (asthma or COPD). Protein analysis in sputum was used to measure plasma protein leakage, and this study indicates that nedocromil sodium reduced this leakage, which may be regarded as an anti-inflammatory effect.

This study shows limited clinical efficacy of nedocromil in patients with partially reversible airways obstruction. There was a statistically significant increase in peak flow and a decrease in inhaled bronchodilator use at night after 12 weeks of treatment with nedocromil, but we found no significant decrease in symptom scores The effect of nedocromil sodium on PEF, however, was small and it remains uncertain whether it is of any clinical relevance. Furthermore, in the placebo group the PEF values were already high at the baseline, which may have obscured any possible improvement during treatment in this group. Significant effects on symptom scores were also not seen in the study by BEL *et al*. [22], but they were reported by WASSERMAN *et al*. [23].

We found no significant improvement of the FEV1 prebronchodilator after treatment with nedocromil, in agreement with other studies [22, 23]. This is in contrast with earlier studies [11], which were mainly performed in allergic patients with asthma. We found that nedocromil tended to improve FEV1 postbronchodilator (overall postrandomization difference: p=0.06), with the largest change from baseline seen after 12 weeks. This increase of FEV1 postbronchodilator suggests that nedocromil has an inhibitory effect on oedema formation and mucus secretion, rather than a relaxing effect on the airway smooth muscles, which is in line with the nonbronchodilating, anti-inflammatory action of nedocromil. We found no effect on histamine PC20 after 12 weeks of treatment with nedocromil.

The limited clinical effects of nedocromil in this study may be considered in relation to the heterogeneous composition of our study group. Also, patients were not stratified for concomitant medication. Only in retrospect were the patients classified as asthma or COPD according to ATS criteria, and it appeared that the nedocromil group contained less asthmatic subjects than the placebo group. Although asthma is supposed to be more easily affected by anti-inflammatory treatment than COPD, a slight beneficial effect in favour of nedocromil was observed. The statistical analysis of the treatment×diagnosis interaction did not reveal diagnosis effects for any of the parameters analysed except for the permeability parameters. Care should be taken, however, before extrapolating the present findings to populations of COPD

patients. Furthermore, it is to be noted that DE JONG *et al*. [24] did not find objective improvement by treatment with nedocromil sodium in patients with COPD.

We were interested to determine whether nedocromil sodium, which has been shown to have anti-inflammatory effects *in vitro* and *in vivo*, might be able to reduce the plasma protein leakage, as measured in SSP. After treatment with nedocromil there was a decrease in the $Q\alpha_2$-m/Q_{alb} with a maximal effect after 4 weeks. This decrease suggests that there is a partial restoration of the size selectivity of the mucosal membrane in the airways [20]. In the retrospective part of the analysis, there were five subjects with asthma in the treatment group *versus* 13 in the placebo group. These numbers gave some support to the findings with nedocromil sodium in the asthma subgroup in this study. Interestingly, nedocromil sodium did have a beneficial effect on the parameters for the permeability of the respiratory membrane, and the effects seemed to be more consistent in time than in the total study group. The present results are in agreement with a recent study on nasal lavage fluid [25], and with the study of MAZZARELLA *et al*. [13] showing a decrease of albumin in BALF after treatment with nedocromil sodium.

We have analysed the relationship between permeability of the respiratory membrane and the number of eosinophils in the peripheral blood. The latter is considered to be an important inflammatory parameter in asthma [26], and there is increasing evidence for a contribution of eosinophils in the inflammatory reactions in chronic bronchitis and in COPD. In particular, at baseline there was a significant correlation between the two surrogate markers of inflammation. We have no explanation for the divergence in the results for $Q\alpha_2$-m/Q_{alb} and $Q\alpha_2$-m/Q_{cp} with respect to the correlation between the changes in these ratios and changes in the number of eosinophils during treatment. In the asthma patients, the correlations were clearer than in the total group, but the divergence was still present.

The precise mechanism of action of nedocromil is still unclear, but the reduction of plasma protein leakage might result from an inhibitory effect on the release of inflammatory mediators from mast cells [27]. Recently, nedocromil has been shown to block the allergen-provoked late increase in both circulating eosinophils and basophils in atopic patients with asthma [28] and to reduce the number of eosinophils in the bronchial mucosa [29], which suggests that nedocromil affects inflammatory mechanisms through inhibition of leucocyte recruitment. Also, an inhibitory effect of nedocromil was found on the immunoglobulin E (IgE) production by B-lymphocytes [30]. In addition, nedocromil may modulate nonadrenergic noncholinergic neural reflex mechanisms: it has been shown that nedocromil can prevent the bronchoconstriction induced by substance P [31, 32].

The maximal effect of nedocromil on plasma protein leakage occurred after 4 weeks of treatment (fig. 2), whereas the maximal effect on FEV_1, PEF and nighttime bronchodilator use occurred after 12 weeks (table 2 and fig. 1). This discrepancy in timing of effects suggests that different mechanisms of action are involved. Another explanation may be that COPD patients react differently from asthma patients, for which there is some evidence when the results are compared with those in asthma alone.

In conclusion, the present study shows limited clinical efficacy of nedocromil sodium in patients with obstructive airways disease and sputum production. The reduction of plasma protein exudation by nedocromil as measured in sputum sol phase suggests that nedocromil has anti-inflammatory properties, and that analysis of sputum might be useful in assessing changes in disease activity in patients with obstructive airways diseases.

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