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Nedocromil sodium inhibits the early and late asthmatic response to exercise

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ABSTRACT: A double-blind, crossover study was carried out to investigate the effect of nedocromil sodium on the dual asthmatic response to exercise challenge.

Nineteen patients with a late response to bicycle exercise were randomly treated on two study days with 4 mg nedocromil sodium or a matched placebo aerosol, 30 min before commencing exercise. Peak flow was measured before exercise, at intervals up to 60 min after exercise, then hourly for up to 13 h.

In 12 of the 19 patients an early reaction to exercise occurred. In 8 of these 12 patients the early reaction could be inhibited by nedocromil sodium ($p<0.01$) although in half of these patients placebo was also shown to be protective. In the case of the late reaction after exercise challenge, 4–13 h after exercise challenge, nine patients were clearly protected by pretreatment with nedocromil sodium ($p<0.01$) when the fall in peak expiratory flow rate was related to the pre-exercise baseline, four patients showed an equal protective effect of placebo and nedocromil sodium, whilst the others were not protected. When the late asthmatic response (fall in peak expiratory flow rate) after exercise challenge was related to control diurnal peak flow values, the number of responses was reduced; the protective effect of nedocromil sodium remained.

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Asthmatic patients who react with bronchoconstriction after exercise challenge may develop an early asthmatic response (EAR) and/or a late asthmatic response (LAR) [1]. During the EAR, lung function starts to deteriorate within 10 min after exercise, shows a maximum fall after 20–30 min and generally disappears within 1–3 h. A LAR can occur, after partial or complete recovery from the EAR, and begins 4–13 h after exercise, decreasing in severity after 12 h and normally resolving within 24 h. The incidence of LARs due to exercise is disputed [2, 3] but the development of these reactions has been linked to release of mast cell-derived mediators and possible inflammatory changes in the lung [4]. Recent reports have increased the controversy over the mechanism of exercise-induced bronchoconstriction [5]. Changes in serum levels of neutrophil chemotactic factors after exercise were not found to correlate with the severity of bronchoconstriction [6] and examination of mediators in bronchoalveolar lavage samples after exercise challenge suggested no involvement of airway mast cells in the EAR [7]. In a study by RUBINSTEIN *et al.* [8] five out of six patients who had shown a dual response to exercise challenge suffered a similar "late" decrease in forced expiratory volume in one second (FEV_1) on a no-exercise control day, suggesting that the LAR might be caused by diurnal variation of airway calibre in conditions of restricted bronchodilator therapy.

Many of the drugs employed in asthma therapy are effective against exercise-induced asthma [6, 9] but in general only the EAR has been studied. In this study, we examined the effect on both EAR and LAR after exercise of a new topical anti-inflammatory asthma treatment, nedocromil sodium (Tilade®, Fisons plc) [10], which is known to prevent both phases of the dual asthmatic response to bronchial antigen challenge as well as the immediate bronchospasm provoked by exercise challenge [11]. We measured bronchoconstriction primarily by the fall in peak expiratory flow rate (PEFR) from the baseline level recorded prior to each exercise challenge, but a no-exercise control day was also included to investigate the possible influence of diurnal variation on the LAR.

Material and methods

Study design

This was a double-blind, randomized, placebo controlled, crossover trial to study the effect of pre-treatment with nedocromil sodium on the EAR and LAR following exercise challenge in a group of patients known to develop a LAR. Subjects were selected on an initial screening day from patients with a documented history of asthma or chronic obstructive pulmonary disease (COPD) [12]. PEFR ($l \cdot min^{-1}$) was measured, using a mini-Wright peak flow meter and recording the best of three measurements, at 10 and 5 min before commencing exercise challenge. The mean of these two pre-exercise readings was taken as the baseline PEFR value for that day.

Exercise challenge was carried out on a bicycle ergometer (Erich Jager, Wurtzburg, Germany) with the workload at 80% of the predicted maximum, adjusted for age, sex and height [13]. Exercise was performed for 8 min, the workload being reduced if necessary, during which time a heart rate of 90% of predicted maximum was achieved. Heart rate was measured by a Siemens Sirecrust 341 monitor (Siemens, Germany). During bicycle exercise each patient wore a noseclip. Ambient conditions were measured using a Hygrotest 6200 (Quartz AG, Zurich, Switzerland): relative humidity was 20–40% and room temperature 20–23°C. Variations of 10% and 2°C, respectively, were permitted during any one patient study day. Using the same meter for all tests, PEFR was measured at 1, 3, 5, 7, 10, 15, 30 and 60 min after the end of exercise, and again at hourly intervals up to 13 h after challenge. A positive asthmatic response to exercise was defined as ≥18% fall in PEFR from the pre-exercise baseline value.

Table 1. – Patient characteristics at admission (n=19)

Variable	Mean value
Age yrs	38±13.6
Sex M/F	7/12
Diagnosis	13 asthma/ 6 COPD
Histamine PC_{20} $mg \cdot ml^{-1}$	1.4±0.3
Baseline FEV_1 *l*	2.47±0.77
% pred	78±24.3
FVC *l*	3.86±0.93
% pred	99±16.7
Atopic status	14 atopic/5 non-atopic
Smokers	5 yes/14 no
Current therapy:	
Antihistamine	7
Inhaled corticosteroid	13
Oral corticosteroid	9
Theophyllines/xanthines	12
Inhaled bronchodilators	13
Oral bronchodilators	2
Sodium cromoglycate	3

Mean ± SD PC_{20}: concentration provoking a 20% fall in FEV_1; FEV_1; forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

The asthmatic response was defined as an EAR at time points from 1–60 min after challenge and as a LAR when the ≥18% fall from pre-exercise PEFR occurred during the period 4–13 h after exercise challenge. Only patients who developed a LAR (with or without an EAR) were randomized to test treatment. Medication was restricted on all exercise challenge days: inhaled bronchodilators were not to be used for a period of 8 h before exercise, nor sodium cromoglycate for a 24 h period. Use of oral bronchodilators was to be avoided during the preceding 48h, and corticosteroid usage was to have been stable for 3 months and to be maintained at a constant level throughout the study period.

On test treatment study days the same exercise challenge procedure was carried out. Thirty minutes before starting exercise, test treatment was taken by inhalation of two puffs of medication from an aerosol can that contained either nedocromil sodium (total dose 4 mg) or a matching placebo. An additional PEFR measurement was taken one minute before the test treatment. Treatment order was randomly assigned by coding sheet and all study days were separated by an interval of 3–12 (usually 4) days.

To investigate the influence of diurnal variation on the LAR to exercise challenge, PEFR readings were additionally taken at the same times of day on a separate control day, when all conditions were similar to the screening day, except that no exercise challenge was carried out. The no-treatment control days were, as with the treatment days, separated by an interval of 3–12 (usually 4) days. The LAR expressed as % fall in PEFR from the equivalent "clocktime" PEFR on this no-challenge control day was also used to examine treatment effects in relation to diurnal variation of PEFR readings, in a secondary assessment made for comparative purposes.

Patients

Out of 86 patients screened, 19 individuals developed a LAR following exercise challenge and were subsequently randomized to test treatment. Seven of these responders showed an isolated LAR whilst the remaining 12 had a dual reaction. A further 21 out of 86 patients showed only an EAR.

The characteristics of the 19 patients who took part in the drug study are summarized in table 1. Nine patients were randomized to the nedocromil sodium/ placebo treatment order group and 10 to placebo/ nedocromil sodium, the two groups being well-matched. Seven patients were male and 12 female, with an age range from 17.8–62.5 yrs. Thirteen subjects were classified as bronchial asthmatics and six as COPD patients [12], the latter distinguished by FEV_1 reversibility <20% predicted after inhalation of 0.4 mg salbutamol. All showed hyperresponsiveness to inhaled histamine (concentration producing a 20% fall in FEV_1 (PC_{20}) <8 $mg \cdot ml^{-1}$) [14]. Five patients were tobacco smokers and continued their usual smoking pattern during the study. After withdrawal

of concomitant medication all patients had a PEFR value ≥55% predicted before commencing exercise challenge. Informed consent to the trial was obtained from all patients, or from the parents of those who were under-age.

Statistical methods

Parametric statistical methods were applied throughout the analyses. Analysis of variance with patient, order and treatment as factors was used to analyse PEFR differences from baseline at each time point. The PEFR data were also summarized for each patient as area under the curve (AUC) of the time course and maximum % decreases from baseline, again using analysis of variance. These summary data were regarded as the primary variables, with PEFR changes at individual time points defined as secondary variables. Two-tailed tests were used throughout, with a significance level of 0.05.

Diurnal PEFR changes based on equivalent "clocktime" control data are presented for comparative reference only, since the stated purpose of the study was to compare the effects of nedocromil sodium and placebo on the fall in PEFR after exercise.

Patients who failed to show an EAR to exercise on the screening day were excluded from analyses of the EAR but included in the LAR analysis.

Results

All 19 patients completed the study treatment days as well as the screening day. No unusual symptoms were reported during the study. Each exercise challenge was carried out at the same time of day for each patient except in one case (patient no. 36) when the two test treatment challenges commenced 40 min later than on the screening day. Screening day results are detailed in table 2. Five patients (nos 2, 4, 13, 34, 35) used bronchodilators on the screening day. All showed a (late) PEFR reduction of 18% or more (table 2). With the exception of patient no. 34, bronchodilator use occurred only at 9 or 10 h post-exercise, and was repeated at the identical times on the two test treatment days; the results of these four patients were included in the analysis. Patients no. 34 and 37 used bronchodilators on the placebo study day but not on the nedocromil sodium day and their data were analysed only up to the point of medication (5 min and 5 h post-exercise, respectively). Since LAR data from patient no. 34 were excluded for this reason, 18 patients in total were analysed for the post-exercise LAR.

Using paired t-tests (sample size = 19) pre-exercise baseline PEFR values showed little variation on the three challenge days: (mean±SD of 366±69; 369±74 and 371±71 $l \cdot min^{-1}$ for screen day, active and placebo treatment days, respectively). On both the treatment days, PEFR values recorded just prior to aerosol treatment (at 31 min before exercise and 21–26 min before the baseline PEFR measurements) were rather lower than baseline ($p<0.05$): means of 355±72 and 356±68 $l \cdot min^{-1}$ for nedocromil sodium and placebo pre-treatment PEFR values, respectively.

Table 2. – Maximum % fall in PEFR from pre-exercise baseline on the initial screening day for patients showing a LAR

Pat. no.	Order group	Baseline PEFR $l.min^{-1}$	EAR max % fall	LAR max % fall
1	2	375	15	33
2*	1	425	53	20
3	1	375	7	33
4*	2	290	4	38
5	1	285	40	44
6	2	390	72	28
7	2	255	37	49
8	1	480	10	21
9	2	495	50	19
11	1	410	44	42
12	2	300	13	30
13*	2	400	55	73
15	1	425	41	27
34	1	320	6	38
35*	2	400	0	21
36	2	285	37	47
37	1	295	39	53
38	2	355	18	18
39	1	395	72	42

Order group: 1 = nedocromil sodium/placebo; 2 = placebo/nedocromil sodium. *no values have been excluded following bronchodilator use by these patients. PEFR: peak expiratory flow rate; LAR: late asthmatic response; EAR: early asthmatic response.

Results of the analyses carried out on absolute differences in PEFR ($l \cdot min^{-1}$) from the pre-exercise baseline at each test treatment challenge are summarized in tables 3 and 4. PEFR changes on the exercise induced asthma (EIA) (no treatment) screen day are included with the treatment group results for reference only.

Early asthmatic reaction after exercise challenge

Twelve patients had recorded an early reduction in PEFR in the period from 1–60 min after exercise (EAR) and were, therefore, included in analysis of the EAR. As outlined in table 2, seven patients (nos 1, 3, 4, 8, 12, 34, 35) did not develop an EAR and were excluded from further analysis of the EAR. Eight of the 12 subjects with an EAR had protection afforded by nedocromil sodium that was different from placebo. In patient no. 7, 11, 37 and 38 placebo and nedocromil sodium had an equivalent protective effect on the EAR. In patient no. 15 there seemed to be little difference between the values in maximal fall of PEFR 1–60 min after the three challenges, when the PEFR values were related to % predicted normal values. This was due to a low baseline PEFR value prior to exercise on the nedocromil sodium challenge day (screen 425, placebo 430, active drug 360 $l \cdot min^{-1}$).

Table 3. – Analysis of absolute decreases in PEFR ($l \cdot min^{-1}$) from pre-exercise baseline mean at each time point post-exercise challenge: EAR (1–60 min), twelve subjects in each group

Treatment	Pre-exercise baseline mean	Absolute decrease from pre-exercise baseline mean at each time point (min) post-exercise challenge								Mean max % fall from pre-exercise baseline	AUC
		1	3	5	7	10	15	30	60		
None (Screen)	369	49.2	80.8	110.4	114.6	122.1	126.3	143.8	115.4	47	7435
Nedocromil sodium	370	-11.3	25.8	24.6	25.4	36.7	23.3	14.2	5.4	13	933
Placebo	382	26.9	60.2	84.0	95.6	112.7	106.9	131.5	90.6	37	6391
Significance of treatment comparison	NS	NS	NS+	*	*	*	*	**	**	**	**

Results of the screen day challenge are shown for reference only. NS: $p<0.05$; NS+: $0.05<p<0.10$; *: $p<0.05$; **:p0.01. PEFR: peak expiratory flow rate; EAR: early asthmatic response; AUC: area under curve; NS: nonsignificant.

Table 4. – Analysis of absolute decreases in PEFR ($l \cdot min^{-1}$) from pre-exercise baseline mean (sample size) at each time point post-exercise challenge: LAR (4–13 h)

Treatment	Pre-exercise baseline mean	Absolute decrease from pre-excercise baseline mean at each time point (h) post-exercise challenge										Mean max % fall from pre-exercise baseline	AUC
		4	5	6	7	8	9	10	11	12	13		
None (Screen)	369 (18)	55.0 (18)	69.7 (18)	67.1 (18)	66.5 (17)	80.6 (17)	99.7 (17)	73.5 (17)	69.4 (17)	74.7 (17)	84.1 (17)	35 (18)	687 (16)
Nedocromil sodium	370 (18)	-14.4 (18)	-0.6 (18)	8.5 (17)	7.4 (17)	7.1 (17)	22.4 (17)	24.4 (17)	19.1 (17)	11.8 (17)	23.4 (16)	12 (18)	116 (16)
Placebo	374 (18)	43.8 (18)	52.4 (18)	61.5 (17)	53.8 (17)	52.9 (17)	52.1 (17)	50.3 (17)	59.1 (17)	52.1 (17)	52.8 (16)	26 (18)	485 (16)
Significance of treatment comparison	NS	**	NS+	*	NS	*	NS	NS	*	NS+	NS	**	NS

Results of the screen day challenge are shown for reference only. NS: $p<0.05$; NS+: $0.05<p<0.10$;*: $p<0.05$; **: $p<0.01$. For abbreviations see legend to table 3.

Nevertheless, these variant individuals were included in the statistical comparison of treatment effects (table 3). For the EAR (table 3) the maximum % fall in PEFR was significantly less ($p<0.01$) with nedocromil sodium (13 %) than with placebo (37 %). The AUC was also significantly better ($p<0.01$) with nedocromil sodium than with placebo during the EAR.

Late asthmatic reaction after exercise challenge

Significant differences ($p<0.05$–$p<0.01$) in favour of nedocromil sodium *vs* placebo treatment continued to occur at individual time points up to 11 h post-exercise (table 4). Also the AUC for the LAR showed a strong trend in favour of the active treatment. It should be noted that only the nedocromil sodium treated patients fully recovered their baseline levels of PEFR following resolution of the EAR. The maximum % fall in PEFR during the LAR (table 4) also reduced significantly ($p<0.01$) after pretreatment with nedocromil sodium (12 %) compared to placebo (26 %). Individual patient results for maximum fall in PEFR after exercise on the (no-treatment) screen day and following active (nedocromil sodium) and placebo test treatments are presented as % fall from pre-exercise baseline (table 5) and as % predicted normal PEFR (table 6).

Table 5. – Maximum percentage fall in PEFR from pre-exercise basel

Patient no.	EAR (1–60 min)			LAR (4–13 h)		
	Screen	Active	Placebo	Screen	Active	Placebo
1	-	-	-	33	15	14
2	54	27	54	22	9	24
3	-	-	-	33	13	22
4	-	-	-	38	-1	-11
5	40	6	40	44	6	40
6	72	5	82	28	-3	35
7	37	17	16	49	42	20
8	-	-	-	21	7	10
9	50	27	48	19	14	10
11	44	4	4	42	1	62
12	-	-	-	30	30	22
13	55	15	61	73	30	55
15	41	22	42	27	22	33
34	-	-	-	-	-	-
35	-	-	-	21	8	15
36	37	0	29	47	20	40
37	39	2	7	39	-7	15
38	18	3	1	18	-16	15
39	72	31	56	42	35	45
Mean	47	13	37	35	12	26
±SD	±15	±11	±26	±14	±15	±18
Sample size	12	12	12	18	18	18

EAR and LAR: maximum % fall in PEFR. Screen: no-treatment day; active: nedocromil sodium. For further abbreviations see legend to table 2.

Table 6. – EAR and LAR PEFR values (*l* min^{-1})related to % predicted normal values

Pat. no.	Pred PEFR	Pre-exercise PEFR % pred baseline			EAR lowest PEFR % pred			LAR lowest PEFR % pred		
		Screen	Placebo	Active	Screen	Placebo	Active	Screen	Placebo	Active
1	430	87	81	93	74	81	98	58	70	79
2	439	99	105	103	46	48	75	77	80	93
3	418	90	89	85	84	79	79	60	69	74
4	440	66	72	81	64	68	48	41	80	82
5	391	73	73	68	44	44	64	41	44	64
6	589	66	83	66	19	15	63	48	54	68
7	437	58	57	55	37	48	46	30	46	32
8	429	112	104	103	100	91	93	89	93	96
9	427	116	112	109	59	59	80	94	101	94
11	378	109	105	94	61	101	90	64	40	93
12	403	74	67	71	65	62	60	52	52	50
13	463	86	71	99	39	28	84	24	32	69
15	625	68	69	58	40	40	45	50	46	45
34	477	67	68	73	63	71	67	-	-	52
35	519	77	77	74	77	79	77	61	66	68
36	362	79	105	83	50	75	83	41	64	66
37	365	81	88	77	49	82	75	38	96	55
38	497	71	85	76	58	85	73	58	72	88
39	530	75	65	95	21	28	66	43	36	62
Mean	435	82	83	82	55	62	72	54	63	70
±SD	±72	±17	±17	±16	±21	±24	±15	±19	±21	±18

Screen: no treatment day; active: nedocromil sodium. For abbreviations see legends to table 2 and 5.

From careful analysis of the data of table 5 it may be concluded that the LAR in patients no. 2, 3, 5, 6, 11, 13, 36, 37 and 38 was blocked by nedocromil sodium considerably more strongly than by placebo. Analysis of the data in table 6 reveals that patients no. 1, 2, 5, 6, 11, 13, 38, and 39 were protected much better by the active drug than by placebo treatment. This discrepancy necessitates some remarks to allow a proper interpretation of the presented results. Firstly, there appeared to be a considerable individual variation in reaction pattern of the patients. Patients could show an apparent placebo response but nevertheless a distinct improvement in PEFR (when expressed as % of the predicted normal value) when on active drug (patient no. 1). Similarly, patient no. 39 showed only a slight protective effect of the drug when the fall in PEFR was related to pre-exercise PEFR, but showed a much stronger effect when related to the % of the predicted normal value. Furthermore, both these patients had much higher baseline PEFR values (expressed as % of the predicted normal value) on the active challenge day. showed significant blockage of the LAR by nedocromil sodium in terms of % fall from baseline PEFR; in three of these patients the % fall in PEFR related to the % predicted normal value after placebo treatment was, however, almost as good (no. 3) or even better (nos 36 and 37) than after active drug treatment. In the latter two patients, however, the baseline PEFR values on the placebo treatment day were very high compared to that on the day of active drug treatment.

To allow for the influence of diurnal variations in PEFR, measurements taken at the equivalent "clocktimes" on a separate, no-challenge control day were also used as baseline values for calculation of maximum % fall in PEFR during the LAR (table 7). These values are only shown for comparison. These data were not used in the statistical comparison of nedocromil sodium and placebo treatment effects on EIA. The group mean maximum % fall in PEFR 4–13 h after exercise, as calculated from the "clocktime" norm, was approximately 12% less throughout than the fall from the pre-exercise baseline. Consequently, the number of LARs was reduced;

Table 7. – Maximum % fall in PEFR (LAR) from pre-execise baseline and a comparison of the maximum % fall in relation to the control PEFR value at the corresponding "Clocktime"

Pat no.	LAR % fall from pre-exercise baseline			LAR % fall from No-exercise "Clocktime" baseline		
	Screen	Placebo	Active	Screen	Placebo	Active
1	33	14	15	34	21	11
2	30	24	9	19	-21	2
3	33	22	13	11	-2	-24
4	38	-11	-1	46	0	-9
5	44	40	6	20	15	-9
6	28	35	-3	24	-3	2
7	49	20	42	0	0	-8
8	21	10	7	12	9	0
9	19	10	14	2	4	10
11	42	62	1	20	50	-11
12	30	22	30	13	6	26
13	73	55	30	73	63	15
15	27	33	22	16	19	24
34	-	-	-	-	-	-
35	21	15	8	7	0	-18
36	47	40	20	17	-15	-33
37	39	15	-7	40	8	0
38	18	15	-16	23	-3	-18
39	42	45	35	36	57	11
Mean	35	26	12	23	11.6	-1.6
±SD	±13	±18	±15	±18	±23.2	±16.2

For abbreviations see legends to tables 2 and 5..

Patients no. 4, 8, 9 and 35 did not show an active drug effect due to apparent placebo activity (tables 5 and 6). Patients no 7, 12 and 15 did not show an active drug effect when the effect was related to baseline PEFR or % predicted normal values, independent of a placebo response. Taken together, nine patients (nos 2, 3, 5, 6, 11, 13, 36, 37 and 38) however, the overall group mean % fall in PEFR on the screen day still reached 23 %, with 10 out of 18 patients showing ≥19 % fall in PEFR). This diurnally-adjusted LAR was considerably reduced by placebo treatment (mean 12 % fall in PEFR) and ablated by nedocromil sodium (mean increase in PEFR of 2 %).

Discussion

This study set out to investigate the preventive effect of nedocromil sodium on exercise-induced bronchoconstriction in patients showing a late phase reaction (LAR) 4–13 h after exercise challenge. The existence of dual reactions to exercise in patients with airflow limitation is of itself a subject of continuing debate and the prevalence of LARs after exercise challenge has been variously reported as 2–60% [1, 15, 16]. It was, therefore, important to make sure the response that we were measuring was real and not artifactual.

This study further substantiates the evidence for the existence of both an EAR and a LAR after exercise challenge in patients with airflow limitation. From a group of 86 asthmatic patients who underwent exercise challenge, 33 developed an EAR, measured as fall from pre-exercise PEFR. Using the same pre-exercise baseline, a total of 19 out of 86 patients developed a LAR. Only 12 out of 86 patients had a dual response, whilst 7 out of 86 had an isolated LAR. Isolated EAR thus occurred in 21 out of 86 of the patients. These LAR incidence figures based on the "standard" fall in PEFR from pre-exercise baseline may have been improved because we looked for LAR in all the patients rather than examining a subgroup known to develop an EAR to exercise: this could be important as 7 out of 19 LAR patients had no preceding EAR. The incidence of LAR was reduced by half when taken as the fall in PEFR from the corresponding "clocktime" value on a no-exercise control day. Using this more valid criterion as a baseline measure, only 10 of the original 86 patients showed a LAR in response to exercise. Even on this basis, however, the incidence of exercise-induced LAR was considerable and cannot be swept aside. It is possible that our patients were not a truly representative population since they suffered from severe asthma and COPD, such that they had to continue their daily corticosteroid therapy during the study. Nevertheless, some were able to develop a LAR after exercise challenge, which could perhaps indicate that the steroid dose was insufficient. It was interesting to find that all six COPD patients challenged had a LAR after exercise; at present we have no adequate explanation for this.

A protective effect of placebo treatment on both the EAR and LAR after exercise challenge was evident, being stronger on the LAR. This introduced the possibility of psychological influences on the LAR, in addition to doubts about its reproducibility. We have partly answered this question by showing the LAR following exercise challenge to be a highly reproducible phenomenon in repeat tests performed 2–13 weeks after the first challenge [17]. In the 12 patients with an EAR after exercise challenge, four patients showed a placebo effect. In the 19 patients with a LAR after exercise challenge, four patients showed a placebo effect and three patients did not show any drug effect at all. One patient with a LAR after exercise challenge showed only a slight drug efficacy. Taken together these data show that although a placebo effect is present, nedocromil sodium effectively blocks both the EAR and LAR after exercise challenge in the majority of the patients investigated.

In view of the fact that the patients maintained their corticosteroid therapy throughout the trial, we were interested to find that nedocromil sodium not only effectively blocked the EAR and the LAR after exercise challenge but that the effect against the LAR was stronger when this was measured from the diurnal equivalent rather than the pre-exercise PEFR. The strongly protective effect of nedocromil sodium against the LAR resulting from exercise challenge appears to tie-in with the efficacy of this compound in preventing the dual asthmatic response to bronchial allergen challenge [18] and suggests the involvement of an inflammatory component in the exercise-induced LAR also.

It is well-accepted, however, that the pathogenesis of EIA is multifactorial. One major component is considered to be increased water loss from the airway lining fluid, creating a hyperosmolar environment in the bronchial mucosa [19], which could be a stimulus for mediator release from resident cells such as mast cell [4]. The inhibitory activity of nedocromil sodium on mucosal mast cells and other resident cells of the airways would again fit in with this explanation [20, 21], which has been countered, however, by the suggestion that exercise increases bronchial obstruction in asthmatics through congestion of the microvasculature [22]. This mechanism could also be moderated by nedocromil sodium, which is known to affect microvascular leakage and neurogenic inflammation in the airways [23].

Whilst both the pathogenesis of EIA and the mechanism of action of nedocromil sodium remain subjects for investigation, our present study confirmed that a proportion of patients with severe asthma and COPD do develop a LAR after exercise challenge and that both this and the immediate EAR are effectively inhibited by pretreatment with a single dose (4 mg) of nedocromil sodium [24, 25]. Why some patients did well and others did poorly on nedocromil sodium is not quite clear to us.

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