

Cromolyn versus nedocromil: Duration of action in exercise-induced asthma in children

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Cromolyn sodium (10 mg), nedocromil sodium (4 mg), and placebo, all delivered by a metered dose inhaler, were compared in their efficacy and duration of action in preventing exercise-induced asthma in children. After a screening test was performed, 13 patients with asthma performed standard exercise tests 20 minutes and 140 minutes after drug inhalation in a randomized, double-blind, crossover study. Both drugs were significantly more protective than placebo after 20 minutes, but no significant difference was seen between cromolyn sodium and nedocromil sodium. No difference between active drugs and placebo was found 140 minutes after inhalation. At these clinically recommended doses both cromolyn sodium and nedocromil sodium provide equal protection against exercise-induced asthma, and the duration of action of both lasts for less than 2 hours. (J ALLERGY CLIN IMMUNOL 1995;96:510-4.)

Key words: Exercise-induced asthma, cromolyn sodium, nedocromil sodium, children

Cromolyn sodium (CGS) and nedocromil sodium (NCS) are antiinflammatory drugs commonly used in the management of asthma, and both are reported to protect most patients with asthma against different specific and nonspecific bronchial challenges.^{1,2} Although they share the same mechanism of action, several in vitro and in vivo studies have recently indicated that NCS is more effective than CGS,³⁻⁷ because the activation of and mediator release from many inflammatory cells appears to be inhibited better by NCS.⁸⁻¹¹

The efficacy of CGS and NCS in the prevention of exercise-induced asthma (EIA) has been demonstrated in adults^{12,13} and in children.¹⁴⁻¹⁶ Despite the theoretic advantage claimed for NCS over CGS, no difference in the effect of these two drugs against EIA has been found.¹²⁻¹⁶ Because no comparative studies are available on the duration of action of CGS and NCS in preventing EIA in children, our study evaluated this specific aspect.

METHODS

The study was double-blind, randomized, crossover, and placebo-controlled. Thirteen subjects (nine male,

Abbreviations used

CGS:	Cromolyn sodium
EIA:	Exercise-induced asthma
FEV ₁ :	Forced expiratory volume in 1 second
MDI:	Metered dose inhaler
NCS:	Nedocromil sodium

four female) ranging in age from 7 to 15 years (mean $\pm$ SD, 10.0 $\pm$ 2.3 years) were recruited. All patients attended the Pediatric Asthma Clinic at Perugia General Hospital, and all had asthma as defined by the American Thoracic Society.¹⁷ They were being treated with different antiasthmatic regimens such as sustained-release theophylline, β -agonists, CGS, NCS, and inhaled steroids; none was receiving therapy with oral steroids. Sustained-release theophylline was withheld for 24 hours, and other drugs were withheld for 12 hours before each exercise test. None of the subjects had had respiratory tract infections in the 4 weeks before the trial. Informed consent was obtained from patients and their parents, and the protocol was approved by the hospital ethics committee.

The screening test consisted of steady-state running for 6 minutes on a treadmill at an incline that would produce a heart rate of at least 85% of the maximum predicted rate for age.¹⁸ All subjects demonstrated a consistent fall in forced expiratory volume in 1 second (FEV₁) of at least 15% from baseline after the test. On 3 separate days each patient was tested, in randomized blinded order, with different treatments inhaled from a metered dose inhaler (MDI): CGS (5 mg twice), NCS (2

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mg twice), or placebo (two puffs). The drugs were administered by a trained physician, and all the patients were skilled in the use of an MDI. The "closed lip" technique was used. The patients performed the exercise test 20 minutes and 140 minutes after every drug inhalation. Each patient always performed the tests at the same time of the day and completed all tests within 10 days.

Room temperature and relative humidity were monitored in a climate chamber. Differences of 1°C in temperature and 5 mg H₂O/L of air in water content on the test days of each patient were considered acceptable.¹⁹ Room temperatures ranged from 21° to 23° C, and relative humidity ranged from 47% to 58% on the different study days.

Pulmonary function was measured by a turbin spirometer (Pocket Spirometer I; Micro Medical Limited, Rochester, Ky.) according to accepted standards.^{20, 21} Predicted normal values for spirometry were obtained from the study of Knudson et al.²² All children were already familiar with the spirometer. Measurements were performed before drug inhalation (baseline value), before every exercise test (preexercise value), and then 3, 5, 10, 15, and 30 minutes after the end of exercise. Heart rate was also measured before and immediately after the exercise. The exercise test was performed only if the baseline FEV₁ was greater than 70% of the mean predicted value for the child's height and if the baseline FEV₁ varied less than 10% from the values obtained on previous test days. The following indexes were calculated from the results of the pulmonary function tests:

[A] Maximum % fall FEV₁ =

$$\frac{\text{Preexercise FEV}_1 - \text{Lowest FEV}_1 \text{ postexercise}}{\text{Preexercise FEV}_1}$$

[B] % Protection FEV₁ = $\frac{P_s - P_t}{P_s}$

where P_s is the percent fall FEV₁ at the screening test, and P_t is the percent fall in FEV₁ after each treatment.

Complete protection was considered to have been obtained if the percentage fall in FEV₁ was within the normal range (<10%).²³ Clinical protection was considered to have been obtained if the percentage fall after receiving the active drug was half or less of the percentage fall after receiving placebo.²⁴

Analysis of data

Analysis of variance for repeated measures and Wilcoxon signed-rank test were used. Differences were considered significant at $p < 0.05$.

RESULTS

All 13 patients completed the three exercise tests.

Baseline lung function

The mean predrug baseline FEV₁ was 1.84 L (105% of predicted value), 1.85 L (106%), and 1.85 L (106%) for CGS, NCS, and placebo, respectively. No statistically significant difference in these values was present, indicating that lung function remained similar throughout the study period.

Changes in lung function after treatment

Before exercise challenge. None of the treatments caused significant changes in FEV₁. Twenty minutes after drug inhalation CGS was 1.85 L, NCS was 1.85 L, and placebo was 1.84 L; 140 minutes after drug inhalation CGS was 1.86 L, NCS was 1.86 L, and placebo was 1.85 L. No statistically significant differences emerged in these preexercise values.

After exercise challenge. Results for percent fall in FEV₁ observed after screening test and after each challenge on 3 days of treatment are shown in Table I.

No significant difference in the percent fall in FEV₁ was observed on the screening or placebo days, indicating that during the period of the study the subjects remained responsive to exercise. On the placebo day, on the second exercise test (140 minutes after treatment) some patients were slightly less responsive, but no subject had a fall in FEV₁ of less than 50% of the value obtained after the first exercise challenge (20 minutes after inhalation). Thus the exercise-induced reduction in FEV₁ was reproducible for individuals.

Both drugs were significantly more protective than placebo (CGS, $p < 0.005$; NCS, $p < 0.01$) after the first exercise challenge (20 minutes), but no significant difference was seen between them. After the second challenge (140 minutes) neither active treatment demonstrated any significant difference compared with placebo, and no difference was observed between CGS and NCS at this time.

The protection percentage from EIA after each challenge on the 3 days of treatment is shown in Table I. After the first challenge both active drugs were significantly more protective than placebo (CGS, $p < 0.005$; NCS, $p < 0.005$), but no statistically significant difference was seen between CGS and NCS. No difference between active drugs and placebo was observed after the second challenge.

Individual protection

After the first exercise challenge complete protection was observed in seven (54%) of 13 patients treated with CGS, in seven (54%) of 13 treated with NCS, and one (8%) of 13 treated with pla-

TABLE I. Maximum percentage fall in FEV₁ after exercise and percentage protection from EIA (in brackets)

Patient No.	Screening	At 20 minutes			At 140 minutes		
		CGS	NCS	PL	CGS	NCS	PL
1	51.4	38.0 (26)	36.5 (29)	53.5 (0)	38.2 (26)	31.8 (38)	35.5 (31)
2	40.2	6.3 (84)	20.1 (50)	22.1 (45)	4.2 (90)	15.0 (63)	21.5 (47)
3	61.4	33.0 (46)	16.7 (75)	35.3 (42)	47.8 (22)	23.8 (61)	43.8 (29)
4	24.8	3.5 (86)	5.0 (80)	29.5 (0)	22.5 (9)	18.7 (25)	22.8 (8)
5	17.6	11.8 (33)	8.4 (52)	9.3 (47)	9.8 (44)	5.6 (68)	6.0 (66)
6	36.0	5.6 (84)	10.1 (72)	18.5 (49)	10.3 (71)	15.5 (57)	10.4 (71)
7	45.3	18.0 (60)	16.7 (63)	52.9 (0)	41.6 (8)	38.5 (15)	35.2 (22)
8	16.3	3.5 (79)	36.6 (0)	19.6 (0)	4.0 (75)	47.0 (0)	30.5 (0)
9	43.8	5.4 (88)	9.2 (79)	28.4 (35)	4.1 (91)	0 (100)	34.7 (21)
10	38.6	54.1 (0)	29.4 (24)	67.4 (0)	58.7 (0)	64.2 (0)	53.6 (0)
11	31.5	11.5 (63)	11.0 (65)	17.9 (43)	13.1 (58)	13.3 (57)	27.7 (12)
12	22.7	17.3 (24)	5.2 (77)	23.4 (0)	24.7 (0)	37.9 (0)	15.9 (30)
13	36.8	0 (100)	0 (100)	24.7 (32)	6.2 (83)	0 (100)	23.5 (36)
Mean	36.9	16.0 (59.4)	15.7 (58.7)	29.6 (22.5)	21.9 (44.3)	23.9 (44.9)	25.5 (28.6)
SD	13.3	16.2 (31.0)	16.8 (27.3)	18.9 (22.1)	18.8 (35.2)	19.1 (35.2)	14.3 (22.4)

PL, Placebo; NS, not significant.

cebo, whereas clinical protection was present in seven (53%) of 13, and seven (53%) of 13, respectively, for CGS and NCS.

The number of protected subjects decreased after the second exercise test. Only six (46%) of 13, three (23%) of 13, and two (15%) of 13 subjects were completely protected by CGS, NCS, and placebo; clinical protection was obtained in five (38%) of 13, and three (23%) of 13, respectively, for CGS and NCS.

DISCUSSION

Our study shows that CGS (10 mg) and NCS (4 mg), administered by a metered dose inhaler, provide similar protection against EIA in children and that this protective effect lasts for less than 2 hours in most patients.

The validity of findings on the duration of a

protective effect of a drug against EIA depends on the reproducibility of the bronchial response to exercise. On the placebo day none of our subjects had a decrease in FEV₁ after the second exercise test that was less than 50% of that recorded in the first test. This finding indicates a good reproducibility for the airway response to exercise. Furthermore, the similarity in values for FEV₁ at both times before exercise demonstrates that a 2-hour interval is sufficient time for patients to spontaneously recover from exercise-induced bronchoconstriction.

Few studies have compared the protective effect of CGS and NCS on EIA.¹²⁻¹⁶ Unfortunately, the methods of inhalation and doses in each study are quite different, making any comparison difficult. The percentage of our children who had complete protection with CGS (54%) and NCS (54%) after

the first challenge concurs with the results obtained when the same dose of the drugs, the same pharmaceutical formulation, and the same method for evaluating the protective effect on EIA were used.^{14, 16} A statistically significant effect of a drug on EIA does not necessarily indicate the effect is clinically important. Therefore we also evaluated the protection percentage against EIA as an index of good clinical control. This analysis yielded the same results as the analysis of the percentage of decrease in FEV₁ itself.

The protective effect of CGS in EIA is dose-related whatever method of inhalation is used. The inhibitory effect of nebulized CGS has been shown to increase with increasing concentrations of the drug from 2 to 40 mg,²⁵ and a similar dose-response effect was demonstrated with a pressurized aerosol at doses from 2 to 20 mg.²⁶ On the contrary, the response to NCS in preventing EIA was not found to be dose-dependent when increasing doses from 0.5 to 20 mg were inhaled through an MDI.²⁷ Thus if we had used higher doses of both drugs, probably only CGS would have provided better protection against EIA, because the NCS dose lies near the top of dose-response curve. This point has important practical implications. The 2 mg dose of CGS, which is ordinarily prescribed in some countries, could be suboptimal for many patients, and in our view a dose of at least 10 mg should be recommended.¹⁶

The results of our study also demonstrate that the duration of protection against EIA afforded by CGS and NCS was short: less than 2 hours for most patients. These data confirm the results of other clinical studies both in adults^{28, 29} and in children.³⁰

As far as we know, ours is the first study to compare the duration of action of CGS and of NCS in preventing EIA in children. König et al.¹³ demonstrated that both CGS and NCS are equally effective against EIA in adults but that NCS may have a somewhat shorter duration of action than CGS. Our results do not, however, confirm that CGS is longer acting. In the König study¹³ different drug formulations were used, and NCS (4 mg) was administered with an MDI, whereas CGS (20 mg) was administered with a Spinhaler (Fisons Corp., Rochester, N.Y.). Comparing the protection of CGS administered with a Spinhaler or with an MDI on EIA, Bar-Yishay et al.³¹ reported that only the Spinhaler provided good protection after 2 hours. Because the doses were not the same, it is questionable whether the aerosol was really less effective.

Increasing the dose of CGS has also been demonstrated to prolong its duration of action. Patel et

al.³² showed that only 10 mg of CGS inhaled through an MDI provided significant protection after 4 hours, because the inhibitory effect of 2 mg had worn off within 2 hours. However, the number of adult patients they studied was limited, and in our opinion these data cannot be simply extended to children, because specific dose-duration studies on the protective effect of CGS and NCS against EIA are lacking for this age group.

In any case, the results obtained in adults are difficult to reconcile with ours. A correct inhalation technique is crucial for optimal deposition of particles in the peripheral airways, but we do not believe the lack of long-lasting protection we observed was due to poor technique, because all our patients were well instructed in use of the MDI.

The discrepancy between our results in children and reports from adult studies suggests that specifically addressed dose-duration trials on the protective effect of both drugs against EIA in children need to be performed in the future.

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