

A double blind trial of the effect of cromolyn sodium on exercise-induced bronchospasm

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Nineteen children with atopic airway disease who had a demonstrable post-exercise decrease in forced expiratory volume in one second (FEV₁) using a standardized stress on a cycle ergometer were treated with disodium cromoglycate (cromolyn sodium) in a double blind crossover study with a placebo control. Significant reduction of post-exercise bronchospasm was obtained by a single dose of 20 mg. of the drug inhaled one hour before exercise; the effect of the single dose was enhanced if preceded by 3 weeks of daily medication. No side effects were detected during the prolonged use of the drug. The significance of cromolyn's effect on the phenomenon is discussed.

In the 4 years since its clinical introduction by Altounyan,¹ disodium cromoglycate (cromolyn sodium, Fisons Corp., Bedford, Mass.) has been extensively studied for its effect on the course of bronchial asthma and on the modification of asthma induced by various challenges. Its effectiveness in blocking bronchospasm produced by exercise has been reported by a number of investigators.²⁻⁷ Limited numbers of patients have been studied, however, and the studies are subject to criticism because the procedures used to produce exercise-induced bronchospasm (EIB) were not standardized, the experiments were not adequately controlled or cromolyn was administered together with isoproterenol. In an attempt to answer these questions and to compare the effect of a single treatment with prolonged treatment, we have designed a double blind crossover study of the effect of cromolyn on exercise bronchospasm in children.

METHODS AND PROCEDURES

Subjects

Eighteen children, from ages 8 to 21 years (mean 13 years), from the Allergy Clinic, Children's Orthopedic Hospital and Medical Center, Seattle, Washington and some private patients referred to the investigators were included if they met the following criteria: (1) diagnosis of atopy—a history of either hay fever or asthma with positive and clinically relevant skin tests, and (2) demonstration of a fall in FEV₁ of greater than 20 per cent following exercise.

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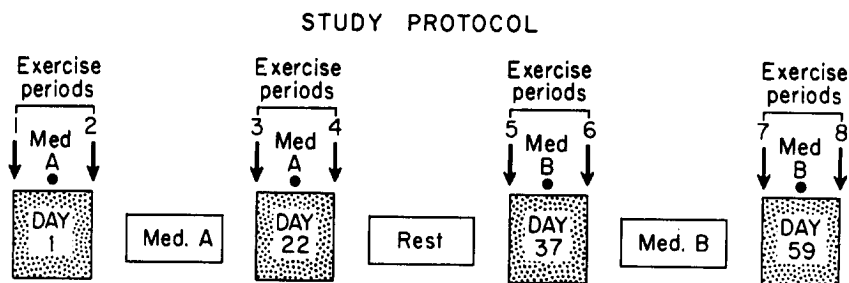


FIG. 1. Exercise periods include resting spirometry, standardized exercise, and post-exercise spirometry; each of the 4 testing days included 2 exercise periods. One hour before Exercise periods 2 and 4, subjects inhaled a single unmarked capsule of Med. A. One hour before Exercise periods 6 and 8 they inhaled a single capsule of Med. B. During the three week periods, "Med. A" and "Med. B," each subject inhaled a capsule of either cromolyn sodium or placebo 4 times a day. During the two week "rest" period they received only their usual medications.

Medications

According to a randomized code known only to the manufacturer, Fisons, subjects were given identical capsules containing either 20 mg. of powdered cromolyn or a placebo powder of lactose and sodium sulfate to inhale. Each subject's usual medications were continued; 2 patients were taking continuous low-dose prednisone.

Study design

For better understanding of the design, certain definitions should be stated: (1) Study period was the entire 8 weeks during which a subject participated. (2) Testing day was one of 4 days when the subject underwent testing. (3) Medication period was 3 weeks during which the subject took either cromolyn or placebo but was not exercised. (4) Exercise period consisted of resting spirometry, standardized exercise, and post-exercise spirometry. (5) Rest period was 2 weeks during which only the subject's usual medications were given.

The design of the study is depicted in Fig. 1. It should be emphasized that each subject was studied before treatment as well as during a cromolyn and a placebo treatment period in a standard double blind crossover protocol. On each of the 4 testing days the patient had an exercise period, received a single dose of either placebo or active medication, and then had another exercise period one hour later. During the first 3 week medication period (Med A in Fig. 1), each subject inhaled one capsule of either placebo or 20 mg. of cromolyn 4 times a day. Following this he returned for another testing day with a final exposure to medication A. After the 2 week rest period each subject returned to repeat the 2 testing periods and medication period with the other unmarked capsule. We tried to prevent identification of the active and placebo capsules by insuring that none of the participants had previous experience with cromolyn and by eliminating a practice period with placebo before the study.

Exercise

All subjects rode a cycloergometer for 5 minutes against a load standardized at a level sufficient to increase the heart rate to 180 beats per minute, or at least 500 Kg. M. per minute per square meter as previously described by Pierson and associates.⁸ Testing was performed in the afternoon, and subjects were asked to omit all medication for 4 hours before testing. If they had significant symptoms on the testing day, exercise was deferred until they were well. McNeil and associates⁹ have shown that if subjects exercised several times in a day, subsequent bronchospastic responses will never be as marked as the first. Accordingly, it was necessary to include a standardizing exercise period on each testing day prior to the subjects' treatment with either placebo or cromolyn (Exercise period 1, 3, 5, and 7 in Fig. 1).

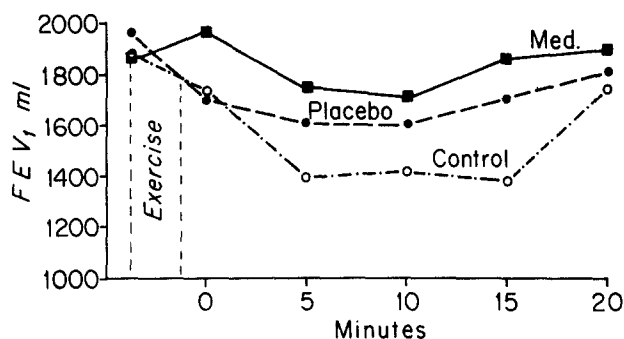


FIG. 2. Means of all subjects' FEV₁ values showing the response to exercise following 3 weeks daily medication with either cromolyn or placebo and a single dose one hour prior to exercise (Exercise periods 4 and 8). Control curve shows FEV₁ response to exercise before exposure to any medication (Exercise period 1).

Pulmonary function

Forced vital capacity (FVC) and FEV₁ were recorded on a Pulmonet spirometer (Godart) at rest, immediately following exercise and at 5, 10, 15, and 20 minutes following exercise.

Statistics

Exercise bronchospasm is a phenomenon that not only is variable among different atopic children with similar vital capacities but also varies from day to day in the individual asthmatic patient. Thus this study was designed to allow each subject to serve as his own control. Each person exercised before any treatment, one hour following a single dose of placebo or cromolyn, and following 3 weeks of daily placebo or cromolyn (prolonged use) as well as another single dose. The fall in FEV₁ in Exercise period 1 was compared with the fall following inhalation of one capsule of cromolyn or placebo (Exercise periods 2 and 6). To evaluate the effects of prolonged use, Exercise period 1 was compared with periods 4 and 8.

Results were expressed as therapeutic index derived from the ratio

$$\frac{\% \text{ fall FEV}_1 (\text{placebo}) - \% \text{ fall FEV}_1 (\text{cromolyn})}{\% \text{ fall FEV}_1 (\text{control})}$$

A positive therapeutic index indicated cromolyn was more effective in that patient, while a negative index indicated the placebo was more effective. The magnitude of the therapeutic index reflected the degree of effectiveness of both. These numbers were then examined by Wilcoxon's Signed Rank Analysis.

Other studies

Subjects were given a symptom score card at the beginning of the study, and the cards were collected at the end of the active and placebo periods. Subjects had physical examinations and laboratory tests on entering the study and at the completion of active and placebo periods. Laboratory tests included a complete blood count, routine urinalysis, serum glutamic oxaloacetic transaminase, blood urea nitrogen, and serum alkaline phosphatase.

RESULTS

Mean FEV₁ values for all subjects during Exercise periods 1, 4 and 8 are shown in Fig. 2. This represents the effects of 3 weeks of chronic therapy plus a single acute dose one hour before exercise. Because these curves represent children with widely varying predicted FVC and FEV, we did not consider

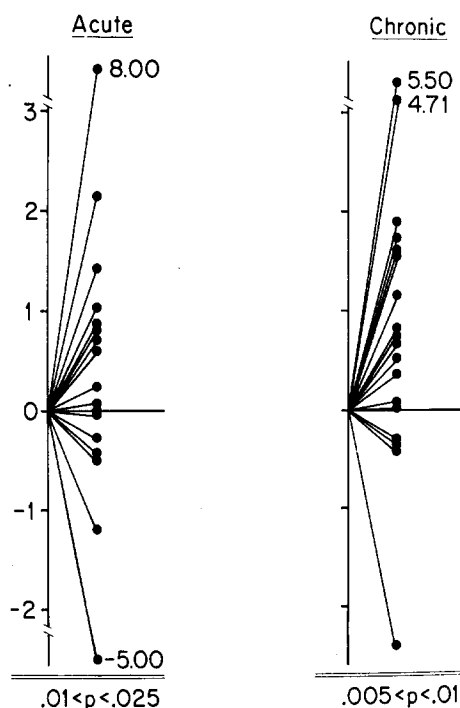


FIG. 3. A therapeutic index (see text for explanation) was plotted for each patient following either a single dose of cromolyn or placebo prior to exercise (acute), or 3 weeks daily medication as well as a single dose one hour prior to exercise. P values were calculated by Wilcoxon's Matched-Pair Signed Rank Analysis.

them statistically valid. They do illustrate 2 points, however. First, confirming the report of McNeil and associates,⁹ response to exercise was less in the second exercise period of the day regardless of the treatment, though at all points cromolyn seemed to have some additional effect compared to placebo. Secondly, the FEV₁ value 10 minute post-exercise, used to calculate the therapeutic index was the best index of change produced by the exercise. Mean curves for the effect of acute premedication, determined by comparing responses in Exercise periods 1, 2 and 6, were similar. Curves for the effect on vital capacity of both acute and prolonged premedication were also similar.

Fig. 3 shows the therapeutic index in which the 10 minute post-exercise FEV₁ was used to calculate per cent fall in FEV₁ for each patient following acute and prolonged pretreatment. The results were found to be statistically significant at the one per cent level following a single dose of cromolyn and at the 0.5 per cent level following 3 weeks of treatment and a single dose on the testing day. Following 3 weeks of treatment with either placebo or cromolyn but before the single dose, post-exercise bronchospasm was suppressed to a similar degree (p value for therapeutic indices was greater than 0.10). Three subjects had a much smaller drop in FEV₁ during the control exercise period than they had following inhalation of either cromolyn or placebo. This resulted in unusually

TABLE I. Summary of previous studies of cromolyn in exercise asthma

Authors	Patients	DSG + Isuprel	Medication	Protocol	Methods of exercise
Muittari and Kreis ²	11 Adults	No	1 Capsule 1 hr. before exercise.	No placebo	Cycloergometer. Exercise to tolerance in 250 Kgm per minute steps.
Rusnakova et al. ³	14 Adults	Yes	2 Weeks chronic placebo and cromolyn without medication immediately before exercise.	Single blind, no placebo	Cycloergometer. Exercise unknown duration at 40 and 80 watts. Measurements during exercise.
Davies, S. E. ⁴	8 Adults	No	15 Minutes, 2 hr. and 4 hr. before exercise.	Not stated, no placebo	8 Minutes running on steps 7" high. Exercised only once each day.
Blackhall and Jones ⁵	16 Children	Yes	2 Capsules ½ and 1 hr. before exercise.	Single blind, no placebo	8 Minutes running on horizontal surface. Exercised only once each day.
Jones and Blackhall ⁶	77 Children	No	4 Days premedication without medication immediately before exercise.	Single blind, no placebo	8 Minutes running on horizontal surface. Exercised only once each day.
Sly, R. M. ⁷	21 Children	No	Capsule 15 min. before exercise; chronic medication without medication immediately before exercise.	Double blind, crossover	Treadmill 8 minutes at 3 mph on 10 degree grade. VC FEV ₁ before, 10 minutes after.

large values for their Therapeutic Index (Fig. 3), but did not effect the statistical analysis.

Although there was no significant difference noted from the symptom score cards, 4 of 5 subjects who thought they recognized the active drug picked cromolyn as the "stronger." Since all children received the same total dose of cromolyn, individual doses thus varied from 1 to 5 mg. per kilogram per day; however, there was no correlation of this with the degree of exercise tolerance produced. No side effects of cromolyn were seen clinically or by laboratory tests.

DISCUSSION

These data confirm the impression of others that cromolyn sodium is effective in modulating EIB. However, several criticisms have been made of previous studies of cromolyn's effect on EIB: (1) Cromolyn capsules also contained isoproterenol; (2) Experimental protocols were usually "single blind" and frequently were not placebo controlled; (3) Exercise procedures varied with investigators and were not usually supported by adequate baseline data; and (4) Little attention has been directed to the effects of prolonged pretreatment. These objections (summarized in Table I) were taken into account, and this study was designed to answer them.

Children were selected who had demonstrated bronchospasm after running on a 5 degree incline. Many had participated in a previous study⁸ on cycloergometer-induced bronchospasm. Unlike Blackhall and Jones,⁵ we found that the cycloergometer will consistently produce post-exercise asthma, provided that the resistance against which the subject works is adequate to increase his heart rate to at least 180 beats per minute for 5 minutes. We found, as did Blackhall and Jones, that exercise after a 3 week course of cromolyn still produced bronchospasm unless another dose was given just before exercise. However, the effect of this single dose was enhanced by prolonged treatment.

Cromolyn's effectiveness in modulating exercise-induced bronchospasm represents a clinical advantage over corticosteroids, which have no effect on this phenomenon.⁹ This point, together with cromolyn's lack of side effects, makes it attractive for long-term treatment of asthma. The effect on exercise bronchospasm provides an objective tool for long-term clinical trials.

Pharmacologically, its effectiveness throws some light both on the mode of action of cromolyn and on the mechanism of EIB. Orange and associates¹⁰ showed that cromolyn will inhibit the antigenic release of histamine and SRS-A from rat mast cells, and that this inhibition is not synergistic with beta agonists or methyl xanthines. This suggests that cromolyn has its effect by independently blocking histamine and SRS-A release, perhaps by stabilizing the mast cell membrane or its granules. Cromolyn's effect on exercise-induced bronchospasm possibly involves the same mechanism, blocking mechanical (physical) release of histamine and SRS-A through mast cell stabilization, since it has no demonstrable direct effects on smooth muscle and does not antagonize the effects of various spasmogens such as histamine, SRS-A, bradykinin, serotonin, or acetyl choline on the guinea pig ileum.¹² These results would also imply that the atopic person's sensitivity to EIB involves the mast cell and mediator release rather than hyperreactive bronchial musculature or adrenergic imbalance.

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