A Perspective on the Role of Cromolyn Sodium as an Antiasthmatic Agent*

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The effectiveness of cromolyn sodium versus placebo for the prophylaxis of asthmatic symptoms was studied by using a double-blind-crossover clinical trial in 20 patients with symptomatic asthma. Eleven patients showed significant improvement in maximum voluntary ventilation, dyspnea index, and maximum mid-expiratory flow rate. Asthma uncomplicated by chronic bronchial infection predominated in this group. The average age was 32 years and the mean residual volume/total lung capacity ratio was 32 percent (SD ± 10 percent). Nine patients failed to show significant improvement in the above noted variables and chronic bronchial infection was an important factor in the asthma of all these patients; the average age was 50 years and the mean residual volume/total lung capacity ratio was 54 percent (SD ± 11 percent). Good agreement between subjective assessment and objective pulmonary function measurements was noted in 18 out of 20 cases. Cromolyn sodium appears to be more effective in young asthmatics with a low incidence of bronchial infection and with only mild pulmonary hyperinflation.

Cromolyn sodium (CS)1 is a new drug in the United States which has been reported to offer a unique means of prophylaxis in asthma. The drug has been evaluated in numerous single and double-blind studies in England, Western Europe, Japan, Australia, Canada and Israel, as well as the United States.1-12 Reports of its efficacy as well as its indications in asthma have varied. Considering these several clinical and experimental results, we designed a double-blind-crossover clinical study of CS which would measure pulmonary function more extensively than in prior studies and hopefully determine which of these tests would be most useful in objectively assessing the clinical course of patients on CS therapy.

The mechanism of action of CS is unlike any previously used mode of therapy. CS is a chromone derivative with an unusual characteristic in that it has been found to specifically inhibit the release of histamine in the human lung following the antigen-antibody reaction.13 It is neither a bronchodilator nor an anti-inflammatory agent. It is distinct from the corticosteroids since there is no evidence that corticosteroids inhibit antigen-antibody union or release of mediators in immediate (type 1) hypersensitivity reactions. It is essentially prophylactic and is of no value if administered following antigen challenge. Approximately 5 percent of an inhaled dose is absorbed via the lung; the remaining portion is trapped in the trachea and major bronchi, then swept up by the ciliary action and swallowed.14

Renal clearance is rapid and the drug is excreted unchanged in the urine and bile after administration by inhalation or injection. It was not found in any tissue or organ in animal autopsy studies. It does not appear to have any effect on bronchial mucous flow and ciliary motility.15

Most studies of CS have dealt primarily with type 1 or immediate (reaginic-IGE mediated) antigen-antibody reactions. Pepys and co-workers16 have shown that CS inhibited the allergic reaction in two patients with bronchopulmonary aspergillosis who gave immediate asthmatic reactions and late febrile
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reactions. The latter type 3 allergic reaction is attributed to the Aspergillus fumigatus antigen. Inhibition of the Arthus type 3 allergic reaction was also shown in three bird fanciers whose symptoms were attributed to avian antigens. CS has been found to specifically inhibit the release of histamine from cutaneous mast cells, and hence to inhibit reactions which depend on the degranulation of mast cells. This is illustrated graphically by the accompanying figure.

MATERIALS AND METHODS

Administration of Cromolyn Sodium and Placebo

The active agent used in this study consisted of capsules containing cromolyn sodium 20 mg and lactose as diluent. Identically appearing placebo capsules containing anhydrous sodium sulfate 5 mg and lactose diluent were used. The sodium sulfate mimics the bitter taste of the active drug. The capsules were administered by inhalation four times per day via the Spinhaler. It was found that the patients could be taught to use this appliance and that a trial period using placebo for practice was unnecessary.

A double-blind-crossover technique of evaluation was used, each patient receiving CS or placebo for one month followed by a one week “no drug” period (to avoid possible carry-over) and then one month on the agent not used in the first month. Order of administration was randomized; physicians and patients were unaware of which agent was being used.

Clinical Material

Twenty-four patients were selected from the clinics of the University of Nebraska Regional Chest Center and from the private practice of an allergist affiliated with the University Medical Center. Selection was made from patients with the diagnosis of severe allergic asthma who had airways demonstrably responsive to bronchodilators and sputum eosinophilia. The patients ranged in age from 13 to 66 years and duration of illness ranged from 4 to 40 years. Those receiving desensitization and/or steroid therapy were asked to maintain the current level of therapy throughout the study. Bronchodilators and antibiotics were permitted on a PRN basis. Four patients were lost to clinical follow-up due to poor cooperation.

Assessment

Each patient received a complete initial workup consisting of history and physical examination, allergy skin testing, complete blood count including absolute eosinophil count, blood chemistry (serum transaminase, alkaline phosphatase and blood urea nitrogen), urinalysis, sputum eosinophils, electrocardiogram, chest roentgenograms (including midecoronal planigram) and baseline pulmonary function testing. The latter included: measurements of vital capacity (VC), total lung capacity (TLC) by the body plethysmograph technique, forced expiratory volume in the first second (FEV₁), maximum voluntary ventilation (MVV), dyspnea index (walking ventilation at two miles per hour divided by maximum voluntary ventilation and expressed as a percent), maximum mid-expiratory flow rate (MMFR), carbon monoxide diffusing capacity by the steady state method and arterial blood gases. The residual volume (RV) was determined by the difference between total lung capacity and vital capacity. Oxygen consumption was also obtained at rest, during ten minutes of exercise and after complete recovery. Clinical improvement was evaluated objectively by repeating blood counts and chemistry, urinalysis, electrocardiogram, VC, FEV₁, MVV, MMFR, dyspnea index and oxygen consumption studies at the end of each monthly course of therapy.

Subjective assessment was accomplished by each patient...
using daily score cards. Wheezing, dyspnea, tightness, cough and sputum production were graded twice daily on a one to ten scale. Use of other medications including antibiotics was also recorded. In like manner, attending physicians recorded the same variables biweekly.

At the conclusion of the double-blind study the patient selected which agent he or she felt better on and the physicians selected the period of best clinical control of symptoms. The drug “code” was then broken and a comparison of placebo versus active agent was made for all tests by statistical analysis, finding “t” for the difference between correlated pairs of observations and using a probability of 0.05 as the level of statistical significance. 

Results

Subjective Evaluations

For the patient’s own ratings of active versus placebo, the difference did not quite reach statistical significance at the level stated above (T-34). However, the rating by the physicians was significant at the 0.005 level (T-20.5) in favor of the active agent. A close examination of the data reveals some justification for this apparent paradox. In two instances patients who were having marked wheezing and dyspnea initially were randomly started on the active agent. Their relief was such that they ranked their initial symptoms as “zero” and continued to do so throughout the course of study. Conversely, the same patients when ranked more critically by physicians had symptom scores as high as five on a ten point scale. This represents an inadequate rating by these two patients which had an obvious effect on results. In 18 out of 20 instances the physician and patient were in agreement subjectively as to the period of most relief and in each case this period was while on CS.

Pulmonary Function Studies

In 12 cases the amount of oxygen consumed during the exercise was less on the active drug, but was not statistically significant (P>0.05). No statistically significant changes were noted in VC or FEV₁ (P>0.05). MVV showed a significant increase on active drug (P<0.05) while MMFR approached statistical significance (P between 0.05 and 0.10). The dyspnea index was improved in 14 patients while on active drug but not at a significant level (P<0.05).

Based on clinical response the patients were divided into two groups. Group A (11 patients) showed significant increase in MVV (P<0.01), of MMFR (P<0.05) and a significant decrease of dyspnea index (P<0.05). Their average age was 32 years and the mean residual volume/total lung capacity ratio was 32 percent with a standard deviation of ±10 percent. Group B (nine patients) showed a nonsignificant change of MVV, MMFR and dyspnea index (P>0.20). Their average age was 50 years and the mean RV/TLC ratio was 54 percent with a standard deviation of ±11 percent. All patients in Group B and only one patient in Group A suffered from chronic bronchial infection.

Toxicity

No evidence of toxicity was elicited from examination of blood count and chemistry or urinalyses. The electrocardiograms and chest roentgenograms remained unchanged throughout the study. Seven patients noted an initial transient throat irritation when on both active and placebo agents, but seemed to adapt to both agents in three to four days after initiation of therapy.

Discussion

The clinical evaluation of asthma and its response to therapy is elusive and complex, a fact universally accepted by clinicians. This is attributed to the nature of the disease process, its varied etiologies, and the patient’s own problem of interpreting the severity of his condition. The design of the present study was such that both objective physiologic testing and subjective impressions by the patient and physician were assessed. It seems significant that in 18 out of 20 cases both patient and physician selected CS as the agent which offered the most relief and freedom from symptoms. These 18 patients also felt the drug had carried them through their most difficult season of the year with less impairment than in comparable periods in the past.

Since it is not readily apparent from the data, a brief comment emphasizing the marked clinical improvement in two patients seems necessary. Both were life-long asthmatics in their mid-twenties. They were inclined toward athletic sports, but were severely restricted in all activities, even to the point of one of them not being able to shower. After being continued on CS therapy for ten months following completion of the double-blind trial both patients have complete absence of symptoms of asthma, and have been performing numerous physical activities which were heretofore impossible.

One patient was later found to have a significantly lowered level of serum α₁ antitrypsin. This correlated with her marked pulmonary hyperinflation. As would be expected she did not improve with CS, although it seems quite likely that she did
have underlying allergic disease (strongly positive skin tests, sputum eosinophils, history of asthma).

Our intent in this study was to investigate available techniques for testing response of the asthmatic airway to this drug. However, it soon became evident that some of the more elaborate and expensive methods of measuring pulmonary function were less useful than frequent monitoring of simple mechanics of breathing (MVV, MMFR, dyspnear index). Improvement of the latter variables corresponded well with physician-patient assessment in distinguishing the placebo from CS in those patients showing CS response. Patients who demonstrated improvement were younger, had only minimal lung hyperinflation and were free of bronchial infection compared with those failing to improve who were older, had moderate to severe lung hyperinflation and all had frequent bronchial infections.

An excellent index of response evolved in this study which should aid the clinician in determining if this drug is indicated in a given patient. The ratio of residual volume to total lung capacity (RV/TLC) provides good evidence of pulmonary hyperinflation and is an excellent yardstick for predicting CS response in the allergic asthmatic. It is our feeling that a patient with a RV/TLC ratio greater than 40 percent is less likely to derive adequate benefit from CS. For this reason the drug offers great hope for the young asthmatic who has not yet sustained damage. An obvious implication of this is the possibility of delaying or even preventing lung damage as the patient becomes older and continues therapy.

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