Chronic Non-specific Lung Disease

THE ROLE OF DISODIUM CROMOGLYCATE IN ITS TREATMENT*

M. A. DE KOCK, M.B., CH.B. (PRET.), F.C.P. (S.A.), M.MED. (INT.) (STELL.), M.R.C.P. (LOND.), AND W. J. C. J. ROSENSTRAUCH, M.B., CH.B. (CAPE TOWN), M.MED. (INT.) (STELL.), *Department of Internal Medicine, University of Stellenbosch, and Karl Bremer Hospital, Bellville, CP*

SUMMARY

The concept (connotation) of the word asthma is discussed. The response to treatment with disodium cromoglycate (Lomudal, Fisons) in 100 patients with chronic airway obstruction is reported.

In selecting patients it is essential to classify them with regard to the mechanism of airways obstruction and, if possible, the aetiology. Such a classification is presented and the role of disodium cromoglycate in the treatment of asthma is discussed.

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The term chronic non-specific lung disease (CNLD) or CARA ('chroniese atipiese respiratoriese aandoeninge' in the Netherlands) includes asthma, bronchitis and emphysema. All these conditions have airways obstruction in common. Airways obstruction is generally considered a troublesome but relatively simple manifestation of lung disease. However, improved techniques for studying lung mechanics and increasing emphasis on lung structure as it relates to function, have shown that the mechanism of obstruction to airflow in the tracheobronchial tree is an exceptionally complex phenomenon.

The mechanisms of airways obstruction may be reversible, as in bronchial and bronchiolar spasm with mucosal oedema, congestion and excessive production of viscid mucus. Obstruction may also be irreversible due to scarring following inflammatory reactions in the bronchi and bronchioles with submucosal gland and goblet cell hyperplasia and destruction of the mucociliary blanket. Irreversible obstruction to expiratory flow may also be caused by expiratory collapse of the large or smaller airways, as in emphysema. Important factors are an inverse relationship between lung volume and airway resistance and the positive intrapleural pressure generated during an active expiratory effort which have an influence on resistance to airflow. Patients with irreversible airways obstruction, e.g. collapsing airways as in emphysema, may have superimposed reversible mechanisms such as bronchospasm, secretions and inflammatory changes.[1]

Before evaluating the effect of any drug on airways obstruction, it is essential to classify the patients according to the mechanisms of airways obstruction (reversible or irreversible) and if possible, the aetiology, because one would not expect any benefit in patients with predominantly irreversible airways obstruction.

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REVERSIBLE MECHANISMS OF BRONCHUS OBSTRUCTION

Narrowing of the bronchial lumen by inflammatory changes and oedema of the mucosa and the wall of the bronchus may be caused by bacterial or virus infections and/or immunological (allergic) reactions. Excessive secretions and exudates are usually associated with inflammatory reactions.

Bronchospasm can be of a reflex nature with the efferent pathway through the vagus. It can also be caused by local action on the bronchial smooth muscle by products of inflammatory and allergic reactions and substances of which the more important are histamine, serotonin, bradykinin, slow-reacting substances, acetylcholine or prostaglandins.

There is also evidence that alpha-adrenergic receptors, which can cause broncho-constriction, are present in the bronchi.[2]

Problem of Classification

To assess the effect of any drug, it is necessary to define fairly accurately the criteria used for choosing the patients included in the trial. It is also necessary to determine, if possible, the degree of reversible and irreversible bronchial obstruction present.

In few, if any, commonly occurring disorders has the problem of definition and differentiation proved as difficult or as contentious as in chronic obstructive diseases of the lung.[3]

Simple chronic bronchitis is a disease characterized by chronic or recurrent increase in the volume of mucoid bronchial secretion sufficient to cause expectoration.

Chronic obstructive bronchitis is defined as a chronic bronchitis in which there is persistent widespread narrowing of intrapulmonary airways, at least on expiration, causing increased resistance to airflow.

Emphysema is defined on an anatomical basis as a disease characterized by structural changes in the lung, causing increase beyond the normal range in the size of the spaces distal to the terminal bronchioles. This anatomical abnormality is commonly associated with increased

resistance to airflow in the lungs, showing little variation either spontaneously or in response to treatment.

Asthma. This word has acquired a wide variety of meanings. It is often employed to denote the physical signs and symptoms associated with bronchial obstruction and is often used synonymously with bronchospasm. This leads to 'asthma' being described as a feature of any disease in which ronchi are audible, including bronchiolitis of all kinds, emphysema and thoracic deformity. It is important to rescue the word 'asthma' from this connotation and to insist that it be used to denote a specific condition. The term asthma should be specifically reserved for spasmodic asthma, the 'extrinsic asthma' of some terminologies. Asthma is a syndrome characterized by atopy (type I allergy) in which the degree of bronchial obstruction is variable and the subject is abnormally sensitive to inhaled allergens or histamine aerosols. Periods of absolute freedom of symptoms may occur spontaneously or after treatment. It is usually associated with a history, or family history, of an allergic condition. Bronchospasm is characteristic of this condition, but the word 'asthma' should not be used as a synonym of the word 'bronchospasm'. Bronchospasm may occur in chronic bronchitis and in emphysema.

These definitions only serve as islands in a sea of confusion and it is difficult, if not impossible, to classify all patients in this group of diseases into watertight compartments. It is clinically much more useful to think in terms of a spectrum of diseases (Fig. 1) with asthma at the one end, emphysema at the other end, and bronchitis somewhere in between. Asthma seldom, if ever, progresses to emphysema unless complicated by chronic bronchitis.[3] The natural tendency is for the disease process to move to the right of the spectrum; the aim of therapy is to arrest this tendency and, if possible, to move it to the left.

Most of the patients with obstructive airways disease can be placed on either the bold solid line (patients starting with asthma usually, but not always, dating from childhood, and characterized by atopy), or on the thin solid line (patients with chronic bronchitis without signs of atopy or allergy) or on the broken line (patients starting with dyspneoa or panacinar emphysema). Bigelow *et al.*[4] observed that 62% of patients diagnosed as emphysema sufferers have a chronic cough occurring before dyspneoa (bronchitic onset); 23% have dyspneoa before cough (dyspnoeic onset), and 15% presented with episodes of wheezing (asthmatic onset).

Bronchospasm is characteristic of asthma but can occur anywhere along the line. When bronchospasm occurs only in association with bronchitis, the condition should be regarded as a variant of chronic bronchitis rather than a type of asthma.

DISODIUM CROMOGLYCATE IN THE TREATMENT OF ASTHMA

During an evaluation in an experimental model, it was proved that disodium cromoglycate is unique in two respects. It acts after antigen-antibody interaction to inhibit selectively the immunological release of a particular chemical mediator[5] and pre-treatment of rats with disodium cromoglycate inhibits the homocytotropic antigen-mediating release of histamine.[6]

Asthma is an example of the type I allergic reaction in which the cell-fixed antibodies seem to be responsible for the reaction. Disodium cromoglycate specifically inhibits the allergic release of spasmogens in an immediate hypersensitivity reaction (type I) in several animal systems.[7] It

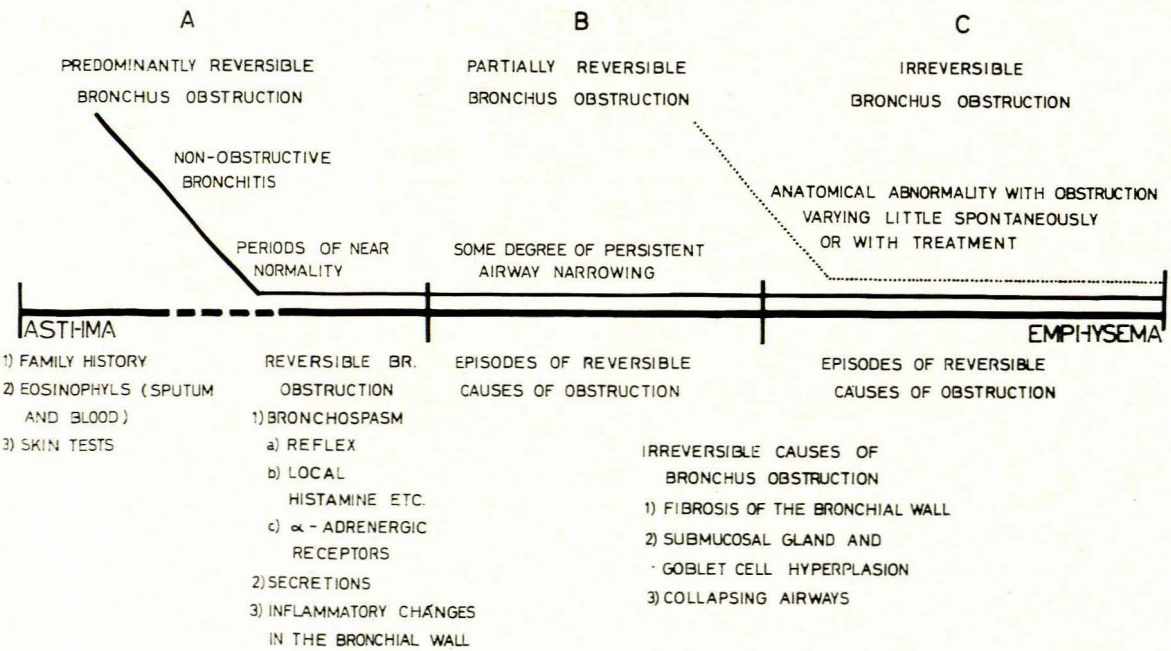

Fig. 1. Spectrum of obstructive bronchopulmonary diseases.

has also been shown to be an effective inhibitor of experimental allergen-induced broncho-constriction in asthmatics.[5,8] However, it is difficult to explain the blocking effect of disodium cromoglycate on exercise-induced asthma by this mechanism. There is evidence that this substance might also prevent broncho-constriction by having a local alpha-receptor blocking effect in the bronchi.[1] Pepys *et al.*[8] also showed that disodium cromoglycate can block the type III or Arthus reaction.

It is reasonable to expect that disodium cromoglycate may be useful in the treatment of true allergic asthma, also in those patients without associated infections, i.e. all patients falling within the range of the thick solid line in Fig. 1 should benefit, with those patients to the left of the scale benefiting most. Conversely, it would be unwarranted to expect any benefit from disodium cromoglycate in patients falling within the range of the thin solid and dotted lines shown in Fig. 1.

Materials and Method

Using the above criteria of selection, the effect of disodium cromoglycate in 100 patients with chronic obstructive airways disease based on allergic mechanisms (patients on the solid line in Fig. 1) was studied over a period from 1 to 13 months.

All patients had episodes of bronchospasm severe enough to interfere with their daily routine. The duration of symptoms varied from 1 to 56 years.

Clinical evaluation of asthma before and after the trial depended on: (*a*) frequency and severity of bronchospastic attacks; (*b*) frequency of administration of bronchodilator aerosols; (*c*) oral bronchodilator drug requirements; and (*d*) steroid requirement.

The degree of improvement was assessed subjectively with each patient instructed in keeping a daily record of his clinical condition during the trial, objectively, by clinical examination, and in 37 cases by means of lung function studies. Most of the patients selected attended the respiratory clinic regularly and had responded poorly to conventional therapy in the past.

The selected patients were grouped into two categories:

A. Those with a significant allergic element (history of atopia, family history, positive skin tests, blood eosinophilia).

B. Those with chronic bronchitis with bronchospasm without obvious allergy.

There were 89 patients in group A of which 12 had uncomplicated allergic asthma, and 77 had episodes of associated bronchitis. There were 11 patients in group B with chronic bronchitis and associated bronchospasm (thin line in Fig. 1).

The diagnosis and sex of the patients are summarized in Fig. 2 and the age distribution is shown in Fig. 3. Allergic asthma was the most common in patients under the age of 30 years, while chronic bronchitis and bronchospasm were the most important features in the age group over 46 years of age.

RESULTS

The effect of treatment with disodium cromoglycate is depicted in Fig. 4. Disodium cromoglycate only was administered to 26 patients in group A (including the 12 patients with no significant infection) and they all showed significant improvement. The remaining 63 patients in this group were previously treated with steroids. In all these patients the dosage of steroids had not been sufficient to control their symptoms completely. Disodium cromoglycate

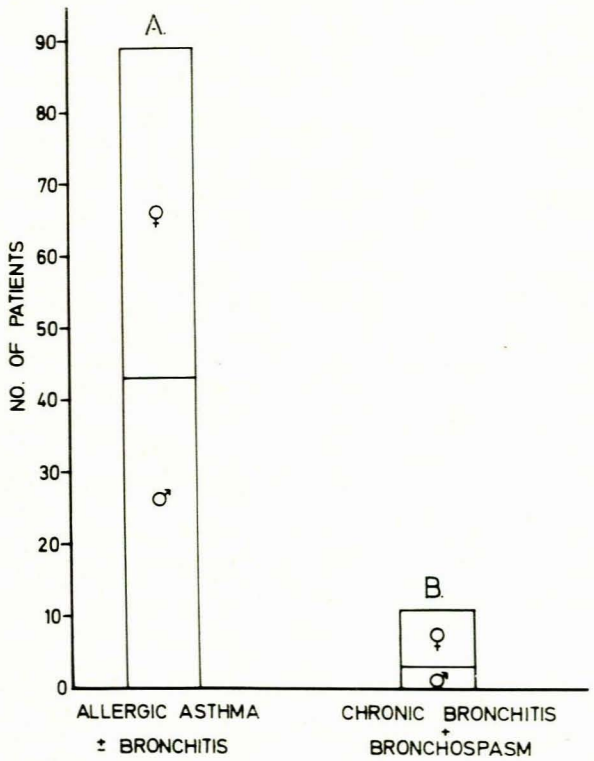

Fig. 2. Diagnosis and sex distribution of patients.

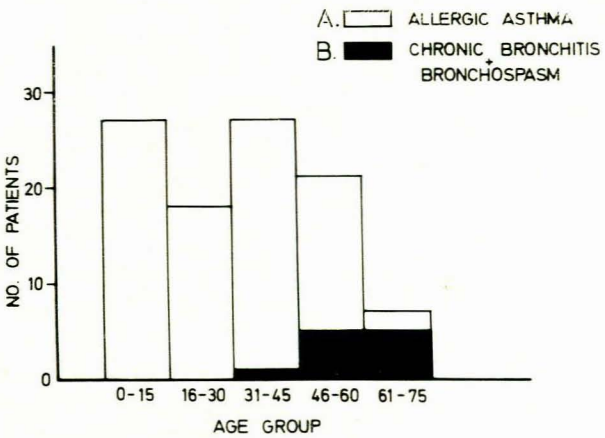

Fig. 3. Age distribution and diagnosis of patients.

was added but the steroid dosage was kept the same. There was improvement in all except 1 of these patients and in 45 cases the steroid dosage could be reduced. The patient who showed no improvement had evidence of irreversible airways obstruction.

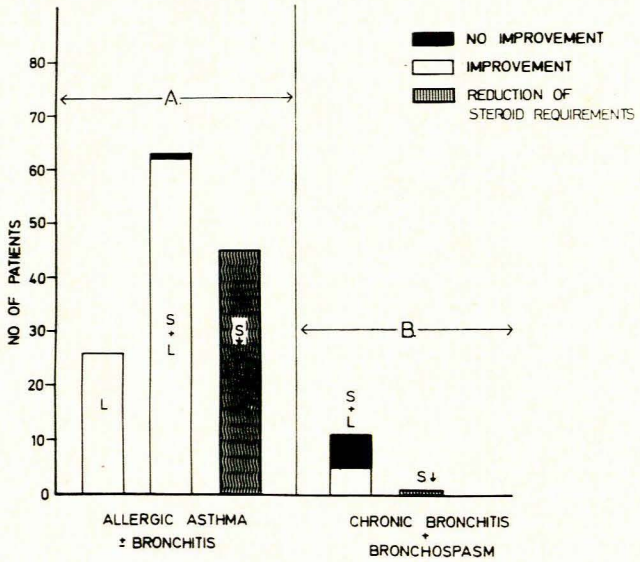

Fig. 4. Result of treatment with disodium cromoglycate.

In group B only 5 of the 11 patients with chronic bronchitis and bronchospasm showed improvement and it was possible in only 1 instance to reduce the steroid dosage.

Because it is well known that the degree of obstruction to airflow in asthma can vary during the day and may be cyclical, it is preferable that if a test like the FEV_1 (1 second vital capacity) is used to assess improvement, to repeat the test at the same time of each day. In 37 patients, of whom 32 belonged to group A and 5 to group B, repeated studies of the FEV_1 were done. Of the patients in group A, 20 showed improvement, 3 no change, 8 slight deterioration. In this group the improvement was statistically significant ($P < 0{\cdot}05$). In none of the 5 patients in group B was there any improvement of the FEV_1 (Fig. 5).

DISCUSSION

Double-blind studies done by others[9-16] have already indicated that disodium cromoglycate is an effective form of therapy in allergic asthma. Asthma is one of a group of diseases classified as chronic non-specific lung disease, which could be regarded as a spectrum of diseases. The selection of patients classified as having asthma is difficult and a new classification is presented. The effectiveness of any drug in the treatment of bronchial obstruction depends on the degree of reversibility of the bronchial obstruction. The more to the right of the spectrum the disease has progressed (Fig. 1), the greater the degree of irreversibility and the lesser the chances of improvement.

Nearly all the patients in whom allergy was the main factor, responded well to disodium cromoglycate. Furthermore, in patients whose symptoms could not be completely controlled with steroids in a safe dosage range (< 15 mg prednisone/day), disodium cromoglycate resulted in an improvement of symptoms (in all but 1 case). In other patients the dosage of steroids could be further reduced. The one patient in whom disodium cromoglycate brought about no improvement had evidence of irreversible airways obstruction.

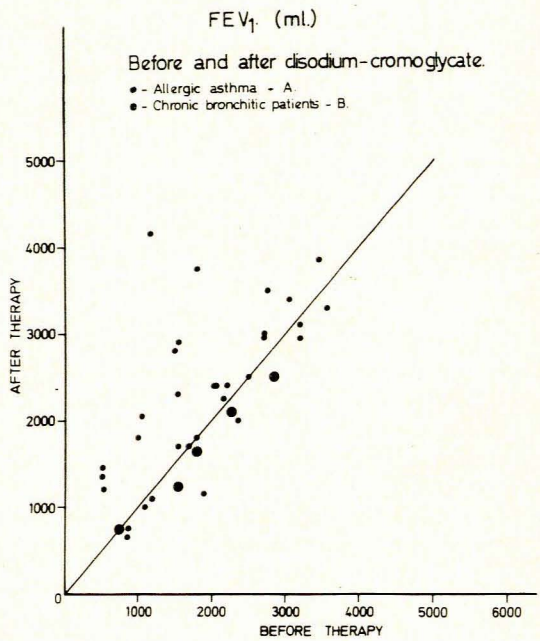

Fig. 5. FEV_1 (ml) of patients before and after disodium cromoglycate.

The response to treatment with disodium cromoglycate in the patients classified as having chronic bronchitis with bronchospasm was unsatisfactory. It is possible that the 5 patients in the group who did show improvement, had a significant allergic component to their asthma and were in retrospect incorrectly classified. The response to disodium cromoglycate might thus possibly be used to classify patients with obstructive airways disease. Those patients who respond to disodium cromoglycate most probably have an allergic element responsible for the bronchospasm.

The mechanism of airways obstruction is complex,[1] and the use of a simple test, the FEV_1, as criterion of improvement should be interpreted with caution. If a significant degree of irreversible bronchus obstruction (e.g. collapsing airways) is present, the FEV_1 may show little or no improvement, even if associated bronchospasm is improved or abolished. There is not always a correlation between the improvement of symptoms and improvement of the FEV_1.

It can be concluded that disodium cromoglycate is of great value in the treatment of patients with allergic asthma.

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