

Sodium Cromoglycate – 25 Years of Success in the Treatment of Asthma



Curriculum Vitae

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Summary

Sodium Cromoglycate (SCG) has established an unparalleled record for efficacy and safety in treating asthma, in children especially, but also in adults. It has been available in South Africa for 25 years and paediatricians in our country observe happier, healthier mothers and children. The attributes of SCG are itemised and many trials, internationally and locally, are evaluated to conclude that asthma is an inflammatory condition and SCG is a major break-through in treating it.

Introduction

Sodium cromoglycate (SCG) has been available in South Africa for 25 years. During this time it has established an unparalleled record for efficacy and safety in the treatment of moderate asthma in both adults and children. The earliest clinical trials stressed the selection of SCG responsive patients based on evidence of allergic asthma. SCG is known to have the following special attributes:

- It antagonises the activation and recruitment of cells involved in the airways inflammation characteristic of asthma – especially mast cells and eosinophils.
- It antagonises the principal pathophysiological events in asthma by blocking bronchial inhalation challenges with antigen, exercise, cold air, fog, pollutants and occupational agents.

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- It blocks both the immediate and late asthmatic reaction to allergen challenge.
- It reduces bronchial hyperreactivity.
- It reduces airway inflammation.
- It has shown efficacy in studies of up to 12 months duration in asthmatics of all ages.
- It has an excellent safety profile with no evidence of major adverse effects after 25 years of clinical use.

SCG should be regarded as an effective anti-inflammatory treatment for asthma.

Background

It is 25 years since the introduction of sodium cromoglycate (SCG) to South Africa in 1969. This remarkable drug has established a firm place for itself especially in the treatment of childhood asthma. In every country which has developed a consensus for the treatment of asthma in children, SCG has been the drug of choice for the mild to moderate asthmatic. The remarkable story of the discovery of SCG, which was developed from khellin by a process of molecular juggling and tested on himself by its pioneer Dr Roger Altounyan, is one of the most remarkable stories in the history of medicine. Initially thought to be a mast cell 'stabiliser', SCG is now regarded as being an anti-inflammatory drug.

It is now established that asthma is an inflammatory condition of the airways. Even those patients with mild disease show remarkable degrees of airways inflammation on endobronchial biopsy.¹ Associated with this inflammation are significant epithelial damage and shedding of epithelial cells caused by mediators

released from eosinophils and neutrophils. In addition there is usually thickening of the basement membrane. Swelling of the mucosa and submucosa is present due to microvascular leakage and there is infiltration of inflammatory cells included among which are eosinophils, mast cells and lymphocytes.⁴

With this appreciation of the inflammatory nature of asthma has come the realisation that treatment must be based on anti-inflammatory drugs. Ideally these drugs should antagonise the activation of cells, involved in the inflammatory process. The drugs should also have a high safety profile and should reverse the pathophysiological events in asthma.

Effects of Sodium Cromoglycate on Inflammatory Cells

The most important inflammatory cells involved in asthma inflammation are mast cells and eosinophils but other cells such as alveolar macrophages, lymphocytes and platelets also play a role.

Since the early days in the use of SCG it has been known that this drug inhibits the release of chemical mediators from mast cells.⁵ These mediators result in inflammation directly and also attract cells to the site of the reaction which aggravate the situation. Much of the early work with SCG was carried out using rat peritoneal mast cells. SCG demonstrated a protective effect against the release of histamine and other mediators induced by both allergic and non-allergic stimulation.⁶ This work has been confirmed in recent studies using primate lung cells challenged with anti-IgE and measuring the release of histamine.⁷

A record for efficacy and safety for treating moderate asthma

Especially for children

Eosinophils, Neutrophils and Monocytes

SCG has been shown to inhibit the activation of eosinophils, neutrophils and monocytes when this activation was caused by either the synthetic bronchial analogue FMLP⁸ or by anti-IgE.⁹ Other studies have demonstrated a direct effect of SCG on these inflammatory cells by various methods.¹⁰

Effect on the Pathophysiological Events in Asthma

SCG has widespread protective effects against the most significant pathophysiological factors commonly associated with asthma. These include a reduction in neurogenic inflammation in studies in both rats and dogs. SCG also inhibits a whole range of bronchial challenge effects in man including antigen challenge, exercise challenge¹¹ and challenges with cold air, fog, sulphur dioxide, sodium metabisulphite, bradykinin and substance P challenges. SCG inhibits both the early and late phase reactions associated with asthma.¹²

A recent review of the long-term effect of SCG on non-specific bronchial responsiveness¹³ showed that long-term treatment with SCG reduced airways responsiveness in patients with asthma. Other studies have also shown that short-term treatment (6 weeks or less) can provide protection against increases in bronchial reactivity during the pollen season.

Effect on Airways Inflammation

In the original trial using SCG, Altounyan¹⁴ stressed the selection of

SCG responsive patients based on evidence of allergic asthma. This was diagnosed by the presence of clumps of eosinophils in the sputum. Kennedy¹⁵ showed that patients who responded best to SCG had numerous eosinophils in their sputum. A reduction in eosinophils occurred with SCG treatment over a 6 week period. Asthmatics are known to have a higher level of albumin in their sputum due to leakage of plasma into the airways. SCG treatment reduces this to normal levels which means that SCG has anti-inflammatory activity.

Backman et al¹⁶ carried out bronchoscopies and bronchial biopsies on 17 children, 6-17 years, with asthma who had been taking SCG for an average of 2 years 3 months. The biopsies were examined for evidence of inflammation. Nine were normal, 6 showed mild inflammation and only 2 showed moderate inflammation. The bronchial mucus was examined cytologically; 13 cases were normal and 4 showed mild inflammation.

Diaz et al¹⁷ carried out broncho-alveolar lavage on allergic asthmatics before and after 8 weeks treatment with SCG and placebo. There was a significant reduction in the SCG treated group compared with baseline values and with placebo.

Efficacy of SCG in the Treatment of Asthma

From its inception certain important characteristics of asthma patients likely to respond best to SCG were identified. These included the fact that SCG was best suited to atopic asthmatics and it appeared to be more effective in young patients.

A controlled study of SCG sponsored

SCG is now regarded as an anti-inflammatory drug

Asthma is an inflammatory condition

by the Drug Committee of the American Academy of Allergy was carried out in 1972.¹⁸ This was a 4-week double-blind, placebo controlled cross over study in asthmatics aged 5-73 years. 252 patients were entered in the study. Overall 77% of patients improved during the SCG treatment phase compared with 38% during the placebo period. Greater treatment effects were seen in patients whose asthma had commenced before the age of 4 years, in those less than 17 years of age, those having had asthma for at least 5 years and patients with allergic and other trigger factors aggravating their asthma.

Another well known study is that of Silverman et al¹⁹ on the long-term effects of SCG and Isoprenaline in asthmatic children. The study was conducted over a period of 1 year. Patients withdrew from the study if control of their asthma was poor. After 12 months 71% of the SCG group still had good control compared with 29% of the Isoprenaline treated group.

These early trials were followed by many others assessing the response to SCG in different population groups and under differing circumstances. Good effects were obtained in various trials using different forms of cromoglycate ranging from the original Spincap form to the later presentations such as the nebuliser solution²⁰ and metered dose inhalers.²¹

Corticosteroid Sparing Effect

Early studies on SCG suggested that the drug had a 'steroid sparing' effect. Significant reductions in oral steroid dosage could be achieved in patients treated on SCG. This was additional support for the anti-inflammatory profile of the drug.

Morrison-Smith and Pizarro²² reported

that 60% of 52 children taking oral steroids for asthma could discontinue steroids and a further 6% could reduce their dose while on SCG treatment.

Dickson and Cole²³ in their 10 year study of 50 children reported that 16 children required regular or intermittent oral steroid therapy in addition to SCG during the first 4 years of treatment. Thirteen of these 16 children who required steroids initially could be weaned by the 7th year of treatment. Only one of the remaining children required steroids by the 10th year of SCG treatment.

Long Term Safety

There have been several studies conducted in double-blind placebo controlled fashion over periods of 12 months to determine the safety of SCG. No serious side-effects were identified.^{19,22}

In addition, there have been 3 major reviews of the safety of the drug during long-term treatment.^{22,24,25} These have involved over 500 patients who took SCG for 3-5 years. No major adverse effects were detected.

In Dickson and Cole's study,²³ 50 children followed for 10 years on SCG treatment showed no clinical or radiological evidence of side-effects and no other adverse effects were observed.

After 25 years of use SCG retains an unparalleled record for efficacy and safety. This has also been the personal observation of most paediatricians treating childhood asthma in this country. Countless children have benefited from its protective anti-inflammatory effect with immense improvement in their lifestyles and in their ability to lead a normal life. It is

Many trials in different forms in different population groups under different circumstances

of interest to note Shores' assessment²⁶ of the efficacy of SCG following the first South African study in asthmatic children. He concluded his report as follows: 'In the majority of cases I was impressed not only by their physical improvement but also by the fact that the children seemed to lose their irritability; they and their mothers were more content – happier. The child, I am sure, because of a subjective feeling of well-being and because he could now run and play normally with his friends. The mother because she slept better and no longer felt that she had a chronically ill child on her hands, who needed constant watching. I have no doubt that SCG is a major break-through in the treatment of childhood asthma.'

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Long-term safety

established in trials over periods of 12 months and even 10 years

A major break-through in childhood asthma – personal experience

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