

EDITORIAL

Inhaled sodium cromoglycate in the management of asthma: should it be consigned to history?

United Kingdom guidelines on the management of asthma were first published in 1990, and revised in 1993 and 1997 [1]. Current guidelines recommend inhaled sodium cromoglycate or inhaled corticosteroids to be given in addition to inhaled short acting beta agonists at step two in the management of asthma in children under 5 years of age. Inhaled sodium cromoglycate is recommended as an alternative to inhaled corticosteroids in step two of the management of chronic asthma in adults and school-children. However, the text of the guidelines states 'There is a disagreement among paediatricians as to whether or not sodium cromoglycate should be introduced as a separate step, prior to low dose corticosteroids'. It comes as a surprise therefore that a recent publication [2] and supporting editorial [3] conclude that there is insufficient evidence that sodium cromoglycate has any beneficial effect in the treatment of childhood asthma.

In this issue of the journal, Larsson *et al.* [4] provide further evidence of the anti-inflammatory profile of sodium cromoglycate. They had previously shown that exposure of healthy volunteers to inhalation of dust in a swine confinement building induced increased body temperature and an intense inflammatory reaction in the upper and lower airways [5]. There was a marked cellular reaction in the airways dominated by neutrophils but also an increase in alveolar macrophages, activated T lymphocytes and a range of pro-inflammatory cytokines in the bronchoalveolar lavage fluid and peripheral blood. Pre-treatment with either intrapulmonary and intranasal sodium cromoglycate or placebo three times daily for 2 weeks before 3-h exposure to swine dust in a swine confinement building demonstrated that inhaled sodium cromoglycate reduced the increase in neutrophils, TNF- α and IL-6 as well as myeloperoxidase and soluble ICAM-1 in the bronchoalveolar lavage fluid.

These anti-inflammatory effects of sodium cromoglycate are mirrored by other recent findings. Bissonnette *et al.* showed that sodium cromoglycate inhibits the release of TNF- α from rat peritoneal cells [6] and Walsh showed inhibition of the release of the same cytokine from human-derived skin slices [7]. Matsuo *et al.* [8], using human lung tissue passively sensitized and then challenged with *Dermatophagoides* antigen, showed that both dexamethasone and sodium cromoglycate reduced the increase in

TNF- α and IL-5 induced by challenge. In a clinical trial comparing nebulized sodium cromoglycate and normal saline in infants at high risk of developing bronchopulmonary dysplasia, Viscardi *et al.* showed that sodium cromoglycate prevented the increase in neutrophils, TNF- α and IL-8 in the lung lavage fluid [9].

An early trial of sodium cromoglycate reported the reduction in the influx of inflammatory cells into the lungs in allergic asthma when Kennedy showed that a reduction in sputum eosinophils correlated with clinical response [10]. Later, Diaz *et al.* reported a reduction in eosinophils in bronchoalveolar lavage fluid [11], and Hoshino a reduction in eosinophils in bronchial biopsy material [12]. The latter investigator also reported a reduction in mast cells and T lymphocytes but no effect on neutrophils. Perhaps of more fundamental interest was the finding by Diaz *et al.* of a significant reduction in house dust mite specific IgE antibodies in bronchoalveolar lavage fluid. More recently two groups of workers have shown that sodium cromoglycate, at dose levels that would be achieved locally *in vivo*, inhibits the spontaneous and stimulated synthesis of IgE antibodies by human B-lymphocytes [13,14]. This effect differs from the effect of corticosteroids that stimulate IgE antibody production [15].

Against this background of further evidence of the anti-inflammatory and anti-allergic actions of sodium cromoglycate on processes involved in allergic inflammation (and more than 30 years of clinical use), it is surprising that the beneficial role of the drug in asthma management should be questioned.

The United Kingdom and international guidelines [16,17] recommend inhaled sodium cromoglycate (or nedocromil sodium) and inhaled corticosteroids on an either/or basis, but this may not be the best way to optimize their use in asthma management. While both are in broad terms anti-inflammatory, they are very different in their pharmacological activity.

Thus, bronchial allergen challenge in allergic subjects results in an immediate and a delayed asthmatic response. Pretreatment with inhaled or oral corticosteroids prevents the delayed but not the immediate reaction to inhaled antigen, whereas inhaled sodium cromoglycate prevents both the immediate and delayed reactions. Both drugs

prevent the associated increase in bronchial responsiveness [18].

Against this body of significant, wide-ranging and relevant anti-inflammatory effects of sodium cromoglycate, it should require strong evidence to 'consign this drug to history'. Examination of the systematic review of the published trials of sodium cromoglycate in childhood asthma on which this suggestion was based [2], shows that across all trials the two variables used to measure clinical efficacy, i.e. the effects on wheeze and cough, demonstrated significant differences from placebo. As others and we have pointed out, there are aspects of this analysis that can be challenged and the conclusions questioned [19].

Perhaps the time has come to reconsider the use and position of sodium cromoglycate in asthma management, not only when used alone but when used in combination with corticosteroids to maximize clinical benefit and minimize the risks of corticosteroid side-effects.

The original discovery of sodium cromoglycate was as a prophylactic agent against inhaled antigens in sensitized individuals. The initial clinical trials were performed on patients with severe asthma persisting despite high-dose oral corticosteroids. Results showed that in the majority of such patients, a reduction in corticosteroid dosage was possible in association with clinical improvement. In their review of their clinical experience with the first 100 patients treated, Altounyan and Howell [20] wrote:

'In view of the apparently similar clinical effects of disodium cromoglycate and corticosteroids, it is tempting to try and equate the effectiveness of the two forms of therapy. But this is not possible as the therapeutic effects of disodium cromoglycate and corticosteroids are not wholly interchangeable. For example, in those patients on maintenance corticosteroid therapy, a minimum dose of corticosteroids is usually necessary, below which disodium cromoglycate is without clinical effect. On the other hand, we have observed patients in whom corticosteroids alone – even in high dosage – could not achieve the same therapeutic response obtained by a combination of a lower dose of corticosteroids together with sodium cromoglycate. From these observations of the effects of sodium cromoglycate and corticosteroids, it appears that at least two processes may coexist in asthma, one being mainly responsive to sodium cromoglycate and the other to corticosteroids.'

It would be a retrograde step if, in the absence of any new and clinically efficacious treatment of asthma, patients had to rely solely on a combination restricted to bronchodilators and corticosteroids, but we fear that this may be the way the guidelines are progressing. There is already much evidence that inhaled sodium cromoglycate has an important part to play in the treatment both of adult and childhood asthma, but its combined use with

corticosteroids to maximize benefit and minimize risk deserves further study.

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