

CORRESPONDENCE

The role of the mast cell in asthma

Sirs

The May 2003 issue of *Clinical & Experimental Allergy* contains a review on 'New insights into the role of the mast cell in asthma' by C E Brightling and colleagues [1]. I was surprised to read in what is otherwise an excellent review, that 'About 20–30% of adult asthmatics respond to cromones'. The reference supporting this statement [2] is another review on the role of mast cells in inflammation. In this latter review, however, no supporting reference is provided for the similar statement, 'Only 20–30% of adult asthmatic patients appear to respond well to drugs in this class'. From where is this figure for responsive patients derived?

The first chromone to be developed for the treatment of asthma, sodium cromoglycate, was developed at a time when double-blind, placebo-controlled trials were becoming the norm and in order to obtain a marketing licence, it was necessary to provide clear evidence of efficacy and safety to the then Dunlop Committee. It is extremely doubtful if evidence of efficacy could be obtained if the response rate was only 20–30%.

Both mast cell reviews cite the first placebo-controlled, double-blind trial conducted with inhaled sodium cromoglycate [3], which was unique in that it was one of the first clinical trials to use a sequential analysis. Such an approach requires a single end-point and in this case it was the clinical response to treatment as judged by the physician. The trial was conducted in adult patients with severe asthma, all of whom required oral corticosteroids for treatment. The first analysis was conducted after 10 patients had completed the trial and it was found that all 10 had responded to treatment with sodium cromoglycate and not to placebo. Perhaps, if the authors of the mast cell reviews had re-read the article they cited, a small doubt might have arisen as to the accuracy of the figure for responsiveness quoted later in the paragraph.

A large number of trials followed this original trial and I will refer to four that looked at clinical response to sodium cromoglycate in adult asthmatics.

Two were planned, organized and conducted by independent bodies, the Medical Research Council in the UK [4], and the American Academy of Allergy in the USA [5]. Both were placebo-controlled and conducted as double-blind trials.

In the UK study, the end-point was failure of test treatment. After 2 months of treatment, the percentage of responders, that is the percentage of patients considered to be satisfactorily controlled, was 73% for the combination of sodium cromoglycate and isoprenaline, 62% for sodium cromoglycate alone, 31% for isoprenaline alone and 19% for placebo. For patients treated with sodium cromoglycate alone, FEV₁ had increased from 55.4% of predicted normal to 72.6% of predicted normal at 1 year.

The US trial was to a 4-week treatment, double-blind, crossover design comparing sodium cromoglycate alone with placebo. Two hundred and fifty-two adult asthmatic patients completed the trial. The physicians conducting the trial considered that 72.4% of patients were 'Very much better' or 'Slightly better' at the end of the sodium

cromoglycate treatment. The figure for the placebo treatment was 31%.

The other two trials have specifically defined response to treatment as one of the end-points. The trial by Patricia Diaz et al. [6], defined response on the basis of improvement in diary-card symptom scores. Fourteen patients (74%) treated with sodium cromoglycate were classed as responders compared to 35% treated with placebo. Bronchoalveolar lavage was carried out on these patients before and after treatment and in the context of inflammation all the patients responding to sodium cromoglycate showed a reduction in mucus eosinophils ($P = 0.005$) in the lavage fluid. This did not occur in the non-responders to sodium cromoglycate and in the placebo group.

If the number of patients in this trial are too small to assess response and non-response to treatment, the final trial I will cite is one in which sodium cromoglycate was compared to one of the oral anti-leukotriene drugs, zafirlukast, and both were compared to placebo [7]. This is also of interest as the producers of the latest British Guidelines on Asthma Management [8] have decided to replace the chromones with oral anti-leukotrienes. This latter trial included 287 patients with over 90 on each treatment. All were adult asthmatics. Response to treatment was defined by both diary-card and pulmonary function criteria. Some might consider the dosage of sodium cromoglycate used in this trial of 8 mg/day too low for an adequate response. Nevertheless, the percentage of patients defined as responders to the three treatments was 70% for zafirlukast, 74% for sodium cromoglycate and 43% for placebo.

I have restricted my examples to sodium cromoglycate as this is still the most widely used of the chromones. However, in the overview analysis of nedocromil sodium I published together with Michael Stevens of all placebo-controlled, double-blind trials conducted up to that date with that chromone, the percentage of patients who found the test treatment to be very or moderately effective in trials where nedocromil sodium was added to existing treatment was 54% for nedocromil sodium and 35% for placebo [9].

The two chromones, sodium cromoglycate and nedocromil sodium are licensed for the treatment of asthma, in both adults and children, in most countries of the world. It is almost impossible that such licenses would have been given if the response rate in adult patients was as low as 20–30%. This is in effect stating that the treatment is no better than a placebo. However, when such a figure gets into the scientific literature, it tends to be perpetuated and this already appears to be happening. It should either be corrected or evidence should be provided to support it.

It is ironic that this should occur in reviews about mast cells. It is doubtful if the importance of the mast cell in allergic inflammation would have been recognized were it not for all the work conducted showing how the chromones can modulate the effect of this cell in disease. Some years ago I had the privilege of editing, together with the

previous editor of this journal, the late Professor Jack Pepys, the proceedings of a meeting entitled 'The Mast Cell: its Role in Health and Disease' [10]. At that meeting the speakers explored, over 3 days, not only the physiology of the mast cell but also its relevance in respiratory diseases, eye diseases, ENT diseases, skin diseases, inflammatory bowel disease and food allergy. Many papers were also presented on the efficacy and usefulness of sodium cromoglycate in these conditions. I do not recall any of the eminent session chairmen nor the 129 speakers casting doubts about the efficacy of the drug at either a cellular or clinical level.

In one presentation, Dr Roger Altounyan, the discoverer of sodium cromoglycate, was invited to review its mode of action. He ended by saying 'Tell me first what asthma really is, then perhaps I could tell you what cromoglycate does to it'. I wonder if 24 years later we are any nearer to answering his question.

References

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The role of the mast cell in asthma. Response to A. M. Edwards by C. Brightling, P. Bradding

We thank Dr Edwards for his interest in our review article [1]. Dr Edwards quotes Dr Altounyan as saying, 'Tell me first what asthma really is, then perhaps I could tell you what cromoglycate does to it'. We believe that we have made some progress in answering Dr Altounyan's question of what asthma really is with our proposal that disordered airway function in asthma is related to the infiltration of airway smooth muscle by mast cells. We acknowledge the great contribution made by Dr Altounyan in the discovery of cromoglycate, and we agree that the role of mast cells in allergic disease gained prominence in the 1960s to the 1970s largely due to the development of cromones.

Over the last two decades the efficacy of cromones has been questioned, and as a consequence of this the GINA guidelines [2] have positioned cromones to be used at step 2 of the guidelines as an additional anti-inflammatory treatment. The BTS asthma guideline advises that nedocromil sodium is beneficial in children between 5 and 12 years of age, but that sodium cromoglycate is not effective in children and cromones are not recommended for adults except for exercise-induced asthma [3]. Dr Edwards' main contention with our review was that our figure of 20–30% response rate to cromones in adult asthmatics is an underestimate. To support his case he refers to a number of studies, all of which show a response rate to cromones of 19–43% above placebo, which is not dissimilar to our view. We do not dispute that cromones have some beneficial effect in a group of patients

with asthma. However rather than revisiting the value of cromones in asthma, the future challenge is to understand the mechanisms that lead to increased mast cell numbers in the airway smooth muscle in asthma. We anticipate that this will lead to novel targets with the potential for new treatments for asthma.

References

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