The clinical efficacy of inhaled nedocromil sodium (Tilade®) in the treatment of asthma

A.M. Edwards*, M.T. Stevens**

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ABSTRACT: Inhaled nedocromil sodium, an anti-inflammatory agent for the maintenance treatment of asthma, has been the subject of many clinical trials but only a proportion have been published.

This paper provides an overview analysis of all known placebo-controlled, double-blind, randomized therapeutic trials. Both single centre and multicentre trials are included. A comparison has been made between the treatment effects of nedocromil sodium and placebo, using six efficacy variables (day and night asthma, cough, mean daily peak expiratory flow rate, inhaled bronchodilator use, clinical lung function (forced expiratory volume in one second) and global opinion of treatment efficacy. One hundred and twenty seven trial centres, involving 4,723 patients, have been included.

The results demonstrate the efficacy of inhaled nedocromil sodium in a variety of patients with asthma. Optimal effects are evident in patients with moderate asthma, currently receiving treatment with inhaled and oral bronchodilators.

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The evaluation of therapeutic agents is a difficult task, not only for the research scientist involved in drug development, but also for the physician who has to make a clinical decision on the basis of published data. Journals tend to favour "positive" findings, and this selective publication, combined with the multiple testing which is carried out in most studies, can produce bias, which may mislead the medical profession. In particular, the evaluation of new drugs in the treatment of bronchial asthma is well recognized as being a difficult task [1, 2]. This is due, in part, to the inherent variability of the disease state, the lack of any objective measure of success and the complications introduced into the interpretation by the use of concomitant medications.

Typically, the size of trial required to detect the clinically meaningful effects of a maintenance therapy for asthma as statistically significant tends to be large. Even when the trial is well designed in advance, the required number of patients is often not achieved. Evaluation from a number of trials or multicentre trials is, therefore, often needed.

The most realistic assessment of the value of a new therapy is likely to come from an initial phase of double-blind studies. The larger this programme of work, the more likely it is that some trials will produce statistically significant results, even if no real treatment effect exists. These "false positives" will tend to be those published in the scientific literature and may overstate the effectiveness of the new drug. The proper assessment of therapeutic efficacy should involve a compilation of all the evidence [3]. The pharmaceutical company concerned is well-placed to do a complete overview of all available data, both published and unpublished.

An overview of this type should have a statistical basis. Statistical analyses carried out on individual trials do not encompass all of the available information or address the complete question. Indeed, there is a paradox in using decision making techniques, such as statistical hypotheses tests, within individual clinical trials, when decisions on efficacy and drug development are based on a package of trials. However, there are difficulties in this approach and it has been suggested [4] that several criteria be met before proceeding: 1) all patients should have been treated for the same disease; 2) the clinical severity of disease should be known; 3) all patients should have received similar test therapy; and 4) the end-points measured should be similar.

We have adopted this approach in the evaluation of an inhaled maintenance therapy for asthma, nedocromil sodium (Tilade® registered trade mark of Fisons plc). Individual studies have indicated statistical evidence of efficacy but, as is common in asthma studies, these indications have not always been in the same
Variables. Many individual studies have been reported. Here, we bring together the data from all known placebo-controlled studies in the programme, in order to demonstrate the value of a complete review, as suggested by Pocock [3].

Methods

The programme of clinical trials consisted of both single centre and multicentre trials. The principle behind the analyses presented in this paper is that each trial centre provides an unbiased estimate of the difference between nedocromil sodium and placebo. Under the null hypothesis that the test treatment has no effect compared to placebo, it would be expected that there would be no statistical differences between the two treatments taken over all trial centres. Conclusions from this analysis have real practical advantages, in that they indicate the efficacy of a treatment as it is likely to be applied in a range of different therapeutic settings.

All double-blind, placebo-controlled studies supplied and analysed by Fisons R & D Laboratories in Loughborough, to date, have been considered. We believe that, up to the time of this analysis, it is unlikely that any other source of inhaled nedocromil sodium and matching placebo was available, so that all completed and analysed, placebo-controlled trials have been included. All were randomized and the majority of these have been of a group comparative design. A small number used a cross-over design and for these, the first treatment period of each order group has been utilized.

The outcome variables have been similar across the range of trials. The scales used, though differing in minor respects, have essentially been similar.

Four classes of variable have been used in the analyses:

1. Global opinion

At the end of treatment, each patient was asked to state their opinion of the effectiveness of the test treatment, using a scale of very effective, moderately effective, slightly effective, no effect, made condition worse. Patients withdrawn owing to treatment failure were assigned the option "made condition worse". For each centre, the percentage of patients demonstrating a good effect (i.e., very or moderately effective) was calculated and the difference between the two treatments compared.

2. Asthma symptoms

Throughout the trials, patients were asked to record the severity of their day and night asthma and cough. The scale for each symptom was 0-4 (0=no symptoms, 4=very severe). In this analysis no scaling was used; each trial had a baseline period and the change from this period to the period between the last two clinic visits has been used for comparative purposes. For four week trials this was the last week of treatment, for six week studies this was the last two weeks, and for 12 week trials the last three weeks.

For the purposes of presentation, day and night asthma scores are added together as a single Day and Night Asthma (scale 0-8).

3. Inhaled bronchodilator treatment

The use of inhaled bronchodilators was recorded night and day on the diary cards. The total 24 h usage was used in the analyses; the data have been handled in a similar fashion to symptom scores.

4. Pulmonary function tests

Morning and evening peak expiratory flow rates (PEFR). These were recorded daily on the diary cards and the data handled in the same way as symptom scores and inhaled bronchodilator usage.

For presentation purposes the mean of the two daily readings is calculated and presented as a mean daily PEFR with mean changes from baseline.

Forced expiratory volume in one second (FEV1). Pulmonary function tests were carried out at each clinic visit; FEV1 has been used as the representative measurement and the change from the baseline visit to the final visit at the end of treatment in the two groups used in the comparison.

Trial design

The trials were of different dose frequency and different design. The two daily dose frequencies (x2 and x4) resulted in a total daily dose of nedocromil sodium of either 8 or 16 mg.

The trials fall into five designs as follows:

Group 1. Test treatment added to baseline treatment consisting of bronchodilators alone. No change to baseline treatment.

Group 2. Test treatment added to baseline treatment consisting of bronchodilators alone. Oral bronchodilators reduced or withdrawn during test treatment.

Group 3. Patients well-controlled on inhaled corticosteroid treatment. Dosage of inhaled corticosteroids reduced prior to baseline period. In this Group, the 16 mg daily dose only was used.

Group 4. Patients inadequately controlled on baseline treatment, which consisted of inhaled corticosteroids. Test treatment added to baseline treatment, which was unchanged during the trial.
Group 5. Test treatment added to baseline treatment consisting of inhaled corticosteroids. Patients selected as being adequately controlled on baseline treatment. Inhaled corticosteroids withdrawn during the trial.

Centres used

The full data set consisted of 196 trial centres. In order to provide an adequate within-centre estimate of the treatment effect, only those centres contributing at least nine patients per treatment group were included.

Statistical analysis

Statistical comparisons were carried out using paired t-tests between treatments considering each centre as a unit. The 5% level of significance (two-tailed) has been used throughout.

Presentation of results

Results are presented as the mean differences across all centres between the effects of nedocromil sodium and placebo on changes from baseline values. As well as the mean difference between treatments, the 95% confidence limits of the mean are presented. Differences in favour of nedocromil sodium are presented as positive values.

Table 1. - Data set used for analysis

<table>
<thead>
<tr>
<th>Dose regimen 8 mg·day⁻¹</th>
<th>Dose regimen 16 mg·day⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Centres</td>
<td>Nedocromil sodium (no. of patients)</td>
</tr>
<tr>
<td>Group 1</td>
<td>31</td>
</tr>
<tr>
<td>Group 2</td>
<td>20</td>
</tr>
<tr>
<td>Group 3</td>
<td>–</td>
</tr>
<tr>
<td>Group 4</td>
<td>7</td>
</tr>
<tr>
<td>Group 5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 2. - Baseline values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scale/units</th>
<th>Groups 1 and 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day and night asthma</td>
<td>0–8</td>
<td>2.47±0.83</td>
<td>2.31±0.44</td>
<td>2.14±0.58</td>
<td>1.06±0.39</td>
</tr>
<tr>
<td>Cough</td>
<td>0–4</td>
<td>1.11±0.45</td>
<td>1.00±0.27</td>
<td>0.88±0.23</td>
<td>0.47±0.19</td>
</tr>
<tr>
<td>Mean daily PEFR l/min⁻¹</td>
<td></td>
<td>359±56</td>
<td>301±47</td>
<td>327±48</td>
<td>399±45</td>
</tr>
<tr>
<td>FEV₁, l</td>
<td></td>
<td>2.27±0.41</td>
<td>1.93±0.23</td>
<td>2.02±0.41</td>
<td>2.49±0.32</td>
</tr>
<tr>
<td>Bronchodilator use puffs·24 h⁻¹</td>
<td></td>
<td>4.78±2.2</td>
<td>7.91±1.96</td>
<td>7.95±2.42</td>
<td>5.96±2.71</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd. PEFR: peak expiratory flow rate; FEV₁: forced expiratory volume in one second.
Day and night asthma

Significant differences are shown (fig. 1) for all groups at both dose levels, apart from Group 4 at 8 mg·day⁻¹. Combining the results of all trials at 8 mg·day⁻¹ and those at 16 mg·day⁻¹ shows both doses to be significantly better than placebo (p<0.001).

Cough

The effects on cough (fig. 2) are significantly in favour of nedocromil sodium in Groups 1, 2 and 3 at both dose levels but not in Group 4 and 5. Combining all trials according to dose shows significant effects overall at both dose levels (p<0.001).
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Mean daily peak expiratory flow rate

Significant effects in favour of nedocromil sodium are shown (fig. 3) at both dose levels when all centres are combined (p<0.001). Significant effects are also shown for Groups 2 and 3, and Group 4 at 16 mg·day⁻¹. The optimal effects are seen in Group 2 at 16 mg·day⁻¹, with the mean difference of nedocromil sodium over placebo being 22±19 l·min⁻¹ (mean±sd).

FEV₁ (clinic)

The changes in FEV₁ measured at visits to the clinic (fig. 4) are more variable, with significant differences in favour of nedocromil sodium overall, at both dose levels in Group 1, and in Group 2 at 16 mg·day⁻¹.

Inhaled bronchodilator use

There was a mean reduction in the use of rescue bronchodilators across all centres (fig. 5) which was significantly in favour of nedocromil sodium (p<0.001). This was also the case in Groups 1, 2 and 3, but not Groups 4 and 5.

The mean reduction overall in the nedocromil sodium group was 1.02 puffs·day⁻¹ at 8 mg·day⁻¹ and 1.07 puffs·day⁻¹ at 16 mg·day⁻¹.

Patients opinion

In fig. 6, the percentage of patients who reported the test treatment as very effective, or moderately effective, is presented as a mean figure together with 95% confidence limits. The figures for nedocromil sodium are significantly in favour (p<0.001) and consistently higher than those for placebo. The largest percentage of patients finding nedocromil sodium very or moderately effective is in Group 2 at 16 mg·day⁻¹, the figure being 60±18%.

Discussion

Assessing the efficacy of a new asthma therapy is not an easy task and conflicting results and conclusions have been reached in different trials with new therapies. This review attempts to assess, in an easily understood format, the results of a complete programme of work on an asthma drug (nedocromil sodium) and reduce the risk of decisions being influenced by a small number of "positive" or "negative" studies. To do this, all available data on nedocromil sodium as compared to a placebo treatment have been used. The only criteria specified were that the studies should be double-blind, placebo-controlled and that each centre should have entered at least nine patients per treatment group. One hundred and twenty seven centres were included and each provided an independent estimate of the treatment difference between nedocromil sodium and placebo.
Examples of each of the five groups have been published as individual trials Group 1 [5-11]; Group 2 [12-17]; Group 3 [18-22]; Group 4 [23-27]; Group 5 [28, 29].

Examination of baseline values shows that existing treatment is an important factor in determining the level of asthma control. The use of inhaled corticosteroids in the treatment regimen provided, in many patients, better asthma control as compared to bronchodilator treatment alone. There was, however, a group of patients (Group 4) who did not have optimal control of asthma using inhaled corticosteroids, as compared to Group 5 and also to patients maintained on bronchodilator treatment alone. The difference between Groups 4 and 5 did not appear to be dependent upon dose of inhaled corticosteroids. Group 5 are the nearest to normal values, with respect to pulmonary function and symptom scores, and the addition of nedocromil sodium or placebo during the first two weeks of the trial did not produce any further improvement (data on file). The rapid withdrawal of inhaled corticosteroids during test treatment in these patients resulted in a worsening of asthma symptoms and a reduction of pulmonary function, which suggests that nedocromil sodium is unable to replace inhaled corticosteroids in these circumstances. In a more recent single centre trial [30], in which the doses of inhaled corticosteroids were reduced in small amounts over a 16 week treatment period, there was no loss of asthma control and it was possible over this time scale to reduce the dose of inhaled corticosteroid by 80% in the nedocromil sodium treated group and by 65% in the placebo treated group.

In Group 3 patients, the reduction of the dose of inhaled corticosteroids by between 50-75% of pretrial levels before the baseline induced a worsening of symptoms and pulmonary function. Nedocromil sodium was able to improve values back to those of the presteroid reduction phase within a four week period. Placebo treatment did not result in a similar improvement and the difference between treatments was significant. This indicates that nedocromil sodium has an inhaled corticosteroid sparing effect, an attribute that has not been demonstrated with inhaled sodium cromoglycate in adult patients [31]. In the final group of patients, whose treatment included inhaled corticosteroids (Group 4) and whose control of asthma was poor, nedocromil sodium provided improvement in asthma severity and pulmonary function at a dose of 16 mg-day\(^{-1}\). Also, in this group, a significantly higher proportion of patients considered nedocromil sodium to be very or moderately effective (45%, p<0.01). This demonstrates that the addition of nedocromil sodium does have a potentially useful place in the management of these difficult patients. It is in patients whose current treatment regimen consisted of inhaled and oral bronchodilator therapy alone that the addition of nedocromil sodium showed a consistent and clinically useful effect in the treatment of asthma. In Group 1, in which current bronchodilator therapy remained unaltered during the addition of test treatment, the dose of 8 mg-day\(^{-1}\) produced statistically significant additional effects both in symptoms and pulmonary function. At the higher dose of 16 mg-day\(^{-1}\) all of the improvements in asthma severity were significant or highly significant, apart from mean daily PEFR. At the higher dose, 56% considered nedocromil sodium to be very or moderately effective.

In Group 2, in which oral bronchodilator therapy was reduced in dose or withdrawn during the test treatment period, a rather different result emerged. In the circumstances of this trial design, the placebo-treated patients showed a worsening of asthma symptoms and reduction in pulmonary function. In contrast, the nedocromil sodium treated patients showed an improvement, the size of which was generally much greater at 16 mg-day\(^{-1}\) than at 8 mg-day\(^{-1}\). Both dose regimens, however, were significantly better than placebo for the majority of variables, with 51% of patients at 8 mg-day\(^{-1}\) and 60% at 16 mg-day\(^{-1}\) considering nedocromil sodium to be very or moderately effective. This latter group of trials indicates that nedocromil sodium can replace all or part of oral \(\beta\)-agonist or oral theophylline therapy with a significantly and clinically useful improvement in asthma control.

One of the purposes of overview analysis or meta-analysis is to make the available data relevant to treatment decisions [14]. In the management of asthma, changes in treatment usually occur when existing treatment fails to produce satisfactory symptom control. In this series of trials it is Groups 1 and 4 that satisfy this criteria: removing existing treatment before the addition of a new treatment (Group 3) or after (Groups 2 and 5) may be of value in demonstrating the efficacy of a new treatment but is not of value to the physician seeking optimal management of asthma. The baseline values of symptoms, pulmonary function and use of inhaled bronchodilators in Groups 1 and 4 are very similar and show less adequate symptom control and pulmonary function below predicted normal. The addition of nedocromil sodium to both groups does result in improvement in all parameters but improvement is greater and achieves more statistical significance compared to placebo in Group 1, those patients taking bronchodilator treatment alone. This suggests that the drug is likely to be of most benefit in patients in this category and of less benefit in patients already taking corticosteroids.

Overall, these results demonstrate a statistically significant treatment effect of nedocromil sodium as compared to placebo, resulting in improved clinical benefit in patients in a wide range of circumstances. Although some individual studies have failed to detect a statistically significant difference between treatment, useful conclusions can be drawn from this overall evaluation.

In summary, the data clearly demonstrate in all response variables that nedocromil sodium has a significant and therapeutically useful effect in bronchial asthma, particularly when used as a first line maintenance treatment in disease of mild to moderate...
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severity. The overview presented here demonstrated the benefits and value of an overall statistical evaluation of a co-ordinated programme of work. We consider that this is a sound, unbiased and essential approach to decision making in drug development.

References

25. Fyans PG, Chatterjee PC, Chatterjee SS. - Effects of adding nedocromil sodium (Tilade) to the routine therapy of patients with bronchial asthma. Clin Exp Allergy, 1989; 19: 521-528.