Inhaled nedocromil sodium in symptomatic young children born prematurely

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The efficacy of a non-steroidal anti-inflammatory agent (nedocromil sodium, NS) has been assessed in young children born prematurely who had recurrent respiratory symptoms at follow-up. In a randomized, double-blind cross-over trial, either two puffs of NS (2 mg puff$^{-1}$) or placebo were administered three times a day via a spacer device and face mask. Fifteen children, median gestational age 27 weeks, birthweight 1100 g and postnatal age 12 months were studied. The symptom score was lower in the last 2 weeks of the active period (median score 26) compared to the run-in period (median score 55) and the last 2 weeks of the placebo period (median score 50), $P<0.01$. The maximum possible symptom score for a 2-week period was 210. Compared to the run-in period, children required fewer days of bronchodilator therapy in the last 2 weeks of the active treatment ($P<0.01$), but not in the placebo period. Although results of functional residual capacity (FRC) measurements were available on only 13 of the 15 children, these did demonstrate a significant change in FRC over the active, but not the placebo, period. These data suggest that NS is a useful prophylactic agent for children born prematurely and who are symptomatic at follow-up.

Introduction

Recurrent coughing and/or wheezing in the first years of life are common amongst children born prematurely (1–3). Although regular inhaled bronchodilators (4,5) can reduce the occurrence of such symptoms, prophylactic medication must be considered in a proportion of these children. Inhaled steroids do reduce symptoms and bronchodilator usage, but there is concern regarding side-effects following long-term use (6–8), particularly in very young children. In some prematurely born children, sodium cromoglycate (SCG) has also been shown to be a useful prophylactic agent (9). Nedocromil sodium (NS, Tilade), which is superior in action to SCG in adults, has been shown to alleviate respiratory symptoms in symptomatic young children born prematurely, and (2) to identify factors influencing any clinical response.

Methods

Children born prematurely with a birthweight less than 2.0 kg were eligible for entry into the trial if they were less than 3 years of age and had not received inhaled steroids. Patients were enrolled into a double-blind placebo controlled cross-over trial of 14 weeks duration if they wheezed and/or coughed on at least 3 days per week during a 4-week period, and remained symptomatic despite administration of regular $\beta$-agonists or ipratropium bromide for at least 2 weeks. Following a 2-week 'run-in' period, they were randomly assigned to receive either 6 weeks of placebo or active therapy. After that 6-week period, the patients switched to the alternative therapy for a further 6 weeks. Both placebo and active treatment were mint tasting and supplied as coded inhalers by Fisons Pharmaceuticals (Loughborough, U.K.). Both were administered as two puffs (4 mg of nedocromil sodium, Tilade) three times a day via a spacer device (Nebuhaler) and a face mask (Laerdal infant mask).

At study entry and at the end of each of the three periods, the patients were examined and a clinical history was taken. The parents completed daily diary cards throughout all three periods. The occurrence and severity of any respiratory symptoms were recorded on the diary card; day- or night-time cough, day- or night-time wheeze, runny nose. Each
category was scored from 0 to 3 (none 0, mild 1, moderate 2, severe 3), giving a maximum score of 210 for a 2-week period.

If the patient was symptomatic, wheezing with or without cough, for more than 24 h, bronchodilator therapy was given. This was either a β2-agonist or ipratropium bromide according to the previous prescription for the child, and was administered in the usual dosage until the child was symptom-free for 24 h. If the patient was admitted to hospital, the respiratory symptoms failed to respond to 48 h of additional bronchodilator therapy, or parents failed to comply with the study protocol, then the child's results were excluded from the analysis.

At the beginning and end of each 6-week period, lung volume was assessed by measurement of functional residual capacity (FRC) by a helium gas dilution technique, as described in detail elsewhere (4). An increase in FRC was taken to indicate improvement, as in the authors' previous studies (4,5,9,16), and increase in FRC has been associated with a reduction in symptoms. To assess the repeatability of FRC measurements, measurements had been made previously in 34 children of similar gestational and postnatal age as the study group at the beginning and end of a 2-week period. In 30 of the infants, FRC was re-measured 4 weeks later. They were all asymptomatic and none had received bronchodilator therapy at the time of the measurement. The coefficient of repeatability was calculated according to the method of Bland and Altman (17). For 2 weeks, it was 15 ml (or 2.3 ml kg⁻¹), and for 6 weeks, it was 18 ml (or 2.6 ml kg⁻¹).

Trial Size

In a previous study, following 2 weeks of regular bronchodilator therapy, 18 children had been enrolled into a cross-over study examining the efficacy of inhaled steroids in prematurely born children (18). The results demonstrated that inhaled steroids compared to placebo therapy reduced the symptom score by 37%. A trial population of 14 children enabled detection with 80% power at the 5% level of a similar reduction in symptom score from the placebo to the active period.

Analysis

The symptom score of the run-in period was compared to the last 2 weeks of each of the 6-week active and placebo periods using a paired Wilcoxon signed rank test. Children who had more than a 37% reduction in symptom score in the last 2 weeks of the active period compared to a similar period in the placebo and run-in periods were considered responders. Such patients were compared to non-responders and differences were assessed for statistical significance using the Wilcoxon rank sum test.

Patients

Twenty children were recruited, but five did not complete the study. One was admitted to hospital and four failed to comply with the study protocol. The 14th and 15th children completed the protocol at the same time. The 15 children (six females and nine males) had a median birthweight of 1100 g (range 570–1960 g), gestational age of 27 weeks (range 23–33 weeks) and postnatal age of 12 months (range 8–27 months). The median duration of neonatal ventilation was 10 days (range 0–149 days) and of oxygen dependency was 43 days (0–3–161 days). Nine children suffered from chronic lung disease (CLD), that is they remained oxygen-dependent beyond 28 days. Seven patients (46%) had a positive family history of atopy. The parents of five children smoked and eight children had previously required admission to hospital for chest-related problems.

The study was approved by the King's College Hospital Ethics Committee.

Results

There was no significant difference between the symptom score of the run-in period and the last 2 weeks of the placebo period (Table 1, Fig. 1). The symptom score, however, was lower in the last 2 weeks of the active period compared to both the run-in period and the last 2 weeks of the placebo period, PS<0.01 (Table 1, Fig. 1). The symptom score was reduced by a median of 45% in the last 2 weeks of the active period compared to the placebo period. Fewer days of bronchodilator therapy were required
in the last 2 weeks of the active period compared to both the run-in period and the last 2 weeks of the placebo period (P<0.01) (Table 1, Fig. 2), but there was no significant difference regarding the days of bronchodilator therapy in the placebo period compared to the run-in period. In eight children, the symptom score was reduced by more than 37% during the last 2 weeks of the active period, compared to both the run-in period and the last 2 weeks of the placebo period. There were no significant differences between children who did and did not respond (Table 2).

Unfortunately, for technical reasons, complete FRC results were only available in 13 children. In those 13 children, however, there was a significant change in FRC over the 6-week active period from a median of 31 ml kg$^{-1}$ (range 20–37 ml kg$^{-1}$) to 36 ml kg$^{-1}$ (range 27–44 ml kg$^{-1}$), P<0.01. No such significant change was seen over the placebo period; the respective FRC results were 33 ml kg$^{-1}$ (range 25–40 ml kg$^{-1}$) and 35 ml kg$^{-1}$ (range 20–42 ml kg$^{-1}$). There was no significant difference between the FRC results at the beginning of the two study periods.

Discussion

A significant reduction in symptom score from the run-in period to the active period was demonstrated. There was no interim washout period, thus the last 2 weeks of each of the two 6-week study periods were compared to avoid contamination of the results by any possible prolonged anti-inflammatory effects of NS. The authors feel that the reduction in symptom score is a valid result as there was also a significant reduction in symptoms in the active period compared to the placebo period, and an indistinguishable mint-flavoured placebo and active therapy were used.

Previously, NS has been difficult to administer in young children due to its burnt taste and smell. In addition, although results were only available from 13 of the 15 children, the significant change in FRC over the active, but not the placebo, period further suggests that NS did have a positive effect on respiratory morbidity in these young children.

In both animal models (19) and humans (20), NS has been shown to inhibit the release of mediators from mucosal mast cells. It also decreases bronchoconstriction in animal models (19). Due to the age of the study population, serial measurements of airway calibre could not be made reliably, but the significantly reduced number of days of bronchodilator usage in the active period would be in keeping with the results from the animal models (19).

There were no significant differences in the characteristics of responders and non-responders. The sample size, however, was small and there were
Table 2 Characteristics of the children who responded to nedocromil sodium compared to the rest of the group

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=8)</th>
<th>Non-responders (n=7)</th>
</tr>
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<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>28 (23-33)</td>
<td>26 (23-33)</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>14 (0-149)</td>
<td>6 (0-20)</td>
</tr>
<tr>
<td>Supplementary oxygen (days)</td>
<td>59 (0-161)</td>
<td>42 (0-363)</td>
</tr>
<tr>
<td>&lt;One year of age (n)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Family history of atopy (n)</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Values given as median (range). n.s., not significant.

trends towards a longer duration of mechanical ventilation and oxygen support in the responders as well as a greater proportion with positive family history of atopy. Increased smooth muscle hypertrophy has been associated with neonatal respiratory support (21), and at follow-up, such patients have an increased airway resistance (22). It is tempting to speculate that such abnormalities may have made them more responsive to NS. The present trial population was less than 3 years of age. This cut-off was deliberately chosen as, up to that age, adverse neonatal factors have a significant association with respiratory morbidity at follow-up (23). In older children born prematurely, however, there is no such clear relationship (24) and thus the response to therapeutic agents is less predictable. In the present population of very young children, postnatal age did not seem to have an influence and even patients less than 1 year of age benefitted from NS.

It is concluded that NS provides useful treatment for some very young children born prematurely. In a previous study (18), the authors assessed the ability of inhaled beclomethasone to reduce recurrent respiratory symptoms and bronchodilator usage in children aged less than 2 years. Although these studies are not directly comparable, it is interesting to note that both agents appeared to have a similar magnitude of effect in reducing respiratory symptoms. Thus, whether NS has advantages over other prophylactic agents now requires investigation in appropriate randomized trials.

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References


