Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease

K Størdal, G B Johannesdottir, B S Bentsen, P K Knudsen, K C L Carlsen, O Closs, M Handeland, H K Holm, L Sandvik

Background: Epidemiological studies have shown an association between gastro-oesophageal reflux disease (GORD) and asthma, and oesophageal acid perfusion may cause bronchial constriction. However, no causative relation has been proven.

Aim: To assess whether acid suppression would lead to reduced asthma symptoms in children with concomitant asthma and GORD.

Methods: Thirty eight children (mean age 10.8 years, range 7.2–16.8; 29 males) with asthma and a reflux index ≥5.0 assessed by 24 hour oesophageal pH monitoring were randomised to 12 weeks of treatment with omeprazole 20 mg daily or placebo. The groups were similar in age, gender, mean reflux index, and asthma severity. Primary endpoints were asthma symptoms (daytime wheeze, symptoms at night, in the morning, and during exercise) and quality of life (PAQLQ). Secondary endpoints were changes in lung function and the use of short acting bronchodilators. At the end of the study a repeated pH study was performed to confirm the efficacy of acid suppression.

Results: The change in total symptom score did not differ significantly between the omeprazole and the placebo group, and decreased by 1.28 (95% CI −0.1 to 2.65) and 1.28 (95% CI −0.72 to 3.27) respectively. The PAQLQ score increased by 0.62 (95% CI 0.29 to 0.95) in the omeprazole group compared to 0.50 (95% CI 0.29 to 0.70) in the placebo group. Change in lung function and use of short acting bronchodilators were similar in the groups. The acid suppression was adequate (reflux index <5.0) under omeprazole treatment.

Conclusion: Omeprazole treatment did not improve asthma symptoms or lung function in children with asthma and GORD.
applied as primary endpoints. The first questionnaire assessed asthma symptoms over the past four weeks (table 1), and the second was the validated Pediatric Asthma Quality of Life Questionnaire (PAQLQ).

Lung function was monitored by spirometry (Jaeger, Germany) according to accepted standards at weeks 0, 6, and 12: forced expiratory volume in 1 second expressed as percent of vital capacity (FEV₁%) and forced expiratory flow at 25–75% of lung volume (FEF₂₅–₇₅) were registered. FEF₂₅–₇₅ was chosen to detect changes in resistance in the smaller airways. The use of rescue medication with short acting β₂ agonists during the past two weeks was recorded at weeks 0, 6, and 12. Other asthma medication was not changed unless required due to exacerbations during the study period. If changes in asthma medication occurred, this was recorded to make necessary corrections in the analyses.

Skin prick tests and specific IgE against common airway allergens (household animals, pollen, house dust mite, cladosporium) and food antigens (egg, milk, soy, fish, peanuts) were performed if this had not been done during the last three years. Total IgE in full blood samples together with cell counts were measured at inclusion, and eosinophilic cationic protein (ECP) was measured at weeks 0 and 12. Patients with total IgE above the age specific cut-off level, increased specific IgE, and/or positive skin prick test were classified as atopic asthmatics.

To confirm that adequate acid suppression (reflux index ≥ 5.0) had been achieved, the consenting participants performed a repeated pH study before the treatment ended.

Statistics and sample size
All changes were expressed as changes from baseline. The treatment and placebo group were compared using two sided t tests for independent samples with a 5% significance level when requirements for a normal distribution could be fulfilled. The Mann-Whitney U test was applied when criteria for normal distribution could not be met. Subgroup analyses were performed for non-atopic and atopic individuals, for those with more severe reflux (RI >10.0), and for those with more severe asthma symptoms at inclusion.

To obtain an 80% chance of detecting a clinically relevant difference between the two groups of one standard deviation in the change in symptom score or PAQLQ, 16 patients were needed in each group. Thus, we aimed to enrol 36 patients to allow for an estimated 10% drop-out rate.

Ethics
The study was approved by the Regional Committee for Medical Research Ethics. Written informed consent was obtained from all participants and parents.

Table 1: Symptoms from the childhood gastro-oesophageal reflux questionnaire during the past week

<table>
<thead>
<tr>
<th>Question</th>
<th>Alternative</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you throw up?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you feel like throwing up or nauseous?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have a burning or painful feeling in the middle of the chest?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have stomach ache?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have stomach ache above the belly button?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have a sour taste, like the taste of throw up, in the mouth?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did it hurt to swallow food or drink?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Box 1: Symptoms from the childhood gastro-oesophageal reflux questionnaire during the past week
RESULTS

Of the initial 165 children with asthma and symptoms of GORD who consented to a pH study, 45 (28%) had an RI >5.0. Three were not eligible for randomisation because of paucity of asthma symptoms as described previously, two withdrew before randomisation, and two had incomplete pH studies.

The remaining 38 children were randomly allocated to omeprazole or placebo treatment. The groups were similar in age and gender distribution, mean reflux index, and asthma severity (table 2). One in each group withdrew because of suspected side effects (headache, worsened asthma symptoms), leaving 18 in each group for final analysis (fig 1).

The change in mean symptom score and PAQLQ from baseline did not differ significantly between the omeprazole and placebo group (table 3). Symptoms in all four subscores listed in table 2 improved, but with no significant effect on asthma severity (table 2). One in each group withdrew because of suspected side effects (headache, worsened asthma symptoms), leaving 18 in each group for final analysis (fig 1).

Analysing atopic (n = 25) and non-atopic (n = 11) children separately showed similar baseline reflux indexes in the two groups (9.3% v 9.4%). In the atopic children PAQLQ improved by 0.55 (95% CI 0.24 to 0.85) in the omeprazole group compared to 0.29 (95% CI 0.29 to 0.84) in the placebo group (p = 0.94). In the non-atopic asthma patients PAQLQ improved by 0.76 (95% CI −0.40 to 1.94) in the omeprazole and by 0.32 (95% CI −0.02 to 0.66) in the placebo group (p = 0.34).

The acid suppression by omeprazole was adequate (RI <5.0) at a repeated pH study in seven of the eight patients consenting to a second pH study, with a mean reduction in RI of 4.9 (2.7–7.1, p = 0.001). In the placebo group the second pH study was abnormal in five of seven patients.

DISCUSSION

The present study did not show any effect of omeprazole treatment on asthma symptoms or quality of life in children with concomitant asthma and GORD. Nor were there any significant effects of oesophageal acid suppression on lung function and the use of β2 agonists.

Studies on omeprazole in adults with asthma have in accordance with our study failed to prove any effect on asthma outcome, although some smaller studies report improvement in peak expiratory flow or asthma symptoms. In children with asthma only one uncontrolled study has been published, reporting on a variety of treatments including proton pump inhibitors.

Most of the previous studies on acid suppression in asthmatics with GORD have not included measurements of the efficacy of GORD treatment, and thus cannot reliably answer the more complicated question whether reduced oesophageal acid exposure improves lung symptoms. We intended to perform a second pH monitoring in all participants to ensure that adequate acid suppression was achieved. Less than half consented to a second study; thus some of the treated children may have received inadequate treatment for their acid reflux. The dosage of 20 mg omeprazole corresponds to 0.25–1 mg/kg, sufficient for the majority of children with GORD. A longer duration of treatment for their acid reflux. The dosage of 20 mg omeprazole corresponds to 0.25–1 mg/kg, sufficient for the majority of children with GORD. A longer duration of

Table 2 Group characteristics at inclusion for 7–16 year old children with asthma treated with omeprazole or placebo for GORD

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole (n = 19)</th>
<th>Placebo (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>10.2 (9.2)</td>
<td>11.3 (11.0)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15/4</td>
<td>14/5</td>
</tr>
<tr>
<td>Reflux index, mean (%)</td>
<td>8.8 (4.0)</td>
<td>9.7 (5.1)</td>
</tr>
<tr>
<td>Not completed (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients with reflux index &gt;10% (n)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Atopic/non-atopic</td>
<td>13/6</td>
<td>13/6</td>
</tr>
<tr>
<td>Asthma symptom score: mean (SD)</td>
<td>5.53 (3.26)</td>
<td>5.95 (2.92)</td>
</tr>
<tr>
<td>PAQLQ*: mean (SD)</td>
<td>5.49 (0.79)</td>
<td>5.32 (0.95)</td>
</tr>
<tr>
<td>GINA classification of asthma severity (step 1/2/3/4)</td>
<td>4/8/7/0</td>
<td>3/6/10/0</td>
</tr>
<tr>
<td>Use of short acting bronchodilators (doses past two weeks): mean (SD)</td>
<td>11.00 (17.23)</td>
<td>8.28 (8.52)</td>
</tr>
<tr>
<td>Patients on daily inhaled steroids (n)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Patients on daily long acting bronchodilators (n)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>FEV1% (mean, median)</td>
<td>88.6 (9.5)</td>
<td>86.9 (7.8)</td>
</tr>
</tbody>
</table>

*PAQLQ, Pediatric Asthma Quality of Life Questionnaire.
†GINA, Global Initiative on Asthma.

Table 3 Outcome measures in children with asthma and GORD treated with omeprazole and placebo

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole (n = 18)</th>
<th>Placebo (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>−1.28 (−2.65 to 0)</td>
<td>−1.28 (−3.27 to 0.72)</td>
<td>1.00</td>
</tr>
<tr>
<td>PAQLQ</td>
<td>−0.62 (−0.29 to −0.95)</td>
<td>−0.50 (−0.29 to −0.70)</td>
<td>0.51</td>
</tr>
<tr>
<td>FEV1% (mean, median)</td>
<td>−1.38 (0.33)</td>
<td>−2.01 (−0.50)</td>
<td>0.77</td>
</tr>
<tr>
<td>FEV25−75 (mean, median)</td>
<td>−0.07 (−0.05)</td>
<td>0.04 (0.05)</td>
<td>0.12</td>
</tr>
<tr>
<td>Rescue medication (mean, median)</td>
<td>−1.9 (0.0)</td>
<td>−1.9 (0.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>ECP baseline</td>
<td>25.9 (14.3, 37.5)</td>
<td>20.2 (12.7 to 27.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>ECP change</td>
<td>1.27 (−5.5 to 8.1)</td>
<td>1.39 (−4.3 to 7.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Values expressed as changes from baseline (week 0) to end of treatment (week 12) with 95% confidence intervals for mean (± 1.96 SEM) unless otherwise stated.
Acid suppression in children with asthma and GORD did not improve asthma symptoms

Subgroups with the more severe forms of asthma and GORD may benefit from acid suppression of asthma symptoms

What this study adds

Acknowledgements

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Competing interests: KS has been reimbursed from AstraZeneca for attending two conferences, and KS and BSB have received fees from AstraZeneca for speaking

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