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

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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 of 5.0 assessed by 24 hour oesophageal pH monitoring were randomised to 12 weeks of treatment with omeprazole 20 mg daily or placebo.

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 0.29 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.

METHODS

Patients

Children between 7 and 16 years of age with doctors diagnosed asthma were asked at their regular outpatient controls from June 2001 to December 2003 to complete a seven point questionnaire addressing gastrointestinal symptoms associated with GORD (box 1). Those with at least one symptom present were, after informed consent, offered a 24 hour pH monitoring.

A reflux index (RI = percentage of total recording time with pH < 4.00) of 5.0 or more was considered abnormal. Inclusion criteria were an abnormal pH study and doctors diagnosed asthma with at least two episodes of asthma symptoms requiring medication over the last six months. Patients with previously known or treated GORD were excluded.

Methods and treatment

The pH study was performed using a Synectics Digitrapper MKIII (Stockholm, Sweden) connected to an antimony electrode introduced transnasally and placed over the third vertebral body above the diaphragm; the position was confirmed by fluoroscopy. After completion of a 24 hour monitoring session, the readings were downloaded to a computer using dedicated software (Medtronic, Copenhagen, Denmark) for analysis and storage.

After eligibility was confirmed, treatment allocation was performed using sequentially numbered containers from the manufacturer (AstraZeneca, Mölndal, Sweden). The patients were randomly allocated to receive either omeprazole 20 mg daily or placebo for 12 weeks. The patients, the caregivers, and the study personnel were blinded to the treatment for the duration of the study.

After a two week run-in period as well as at the end of treatment, two separate questionnaires were completed and
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.
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 to end of treatment in both groups (table 3) did not differ significantly between the omeprazole and 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,24–26 though some smaller studies report improvement in peak expiratory flow or asthma symptoms.27–29 In children with asthma only one uncontrolled study has been published, reporting on a variety of treatments including proton pump inhibitors.30

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.31 A longer duration of 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.

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### 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 (mean, 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 (SD)</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>
<thead>
<tr>
<th>What is already known on this topic</th>
<th>What this study adds</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Epidemiological studies have repeatedly shown an association between GORD and asthma</td>
<td>- Acid suppression in children with asthma and GORD did not improve asthma symptoms</td>
</tr>
<tr>
<td>- Acid perfusion of the oesophagus may induce bronchoconstriction</td>
<td>- Subgroups with the more severe forms of asthma and GORD may benefit from acid suppression of asthma symptoms</td>
</tr>
</tbody>
</table>

Acid suppression in children with asthma and GORD may benefit from acid suppression of asthma symptoms. A causal relation between acid reflux and asthma remains unproven.

ACNOWLEDGEMENTS
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