A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-oesophageal reflux

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ABSTRACT: In order to study the importance of gastro-oesophageal reflux (GOR) as a trigger of asthma the effect of inhibition of gastric acid secretion on asthma was assessed in a double-blind, cross-over, placebo-controlled trial over four weeks in 37 children and adolescents (mean age 14 yrs) with bronchial asthma. Ranitidine 300 mg, (150 mg if B.W. was <40 kg) was given as a single evening dose during four weeks. In previous investigations 18 of the 37 patients had been shown to have pathological GOR by 24 h pH monitoring in the oesophagus. The remaining 19 patients with normal GOR served as controls for possible effects of ranitidine on asthma, not related to reduction of GOR. A modest (30%) but statistically significant reduction of nocturnal asthma symptoms was produced by ranitidine in the patients with pathological GOR when compared to those with normal GOR. There was a significant correlation between the improvement in asthma symptoms and the degree of acid reflux. Side-effects of ranitidine were negligible. Acid reflux appears to be only a weak stimulus for bronchoconstriction in children and adolescents with bronchial asthma and pathological GOR. Further confirmative trials with more potent inhibitors of gastric acid secretion are, however, warranted.


Patients and methods

Forty two children and adolescents with bronchial asthma were asked to take part in a randomized, double-blind, placebo-controlled, cross-over study of the effect of ranitidine (150–300 mg) taken orally once a day in the evening over four weeks. They had all previously undergone a 24 h two level pH monitoring of the oesophagus 0–14 months (mean 3.3 months) prior to the present ranitidine trial, in another study aimed at elucidating the prevalence of pathological GOR in children and adolescents with moderate or severe bronchial asthma [21]. They had also been investigated with an oesophageal acid perfusion test (APT) [8] 3.5–20 months (mean 9.9 months) before the ranitidine trial. Forty of the 42 subjects agreed to participate and 37 subjects, 22 males and 15 females, completed the study (table 1). All participants were using regular asthma medication (table 1) and all of them inhaled beta-agonists when required.

Pathological gastro-oesophageal reflux (GOR) and oesophageal dysfunction (OD) are common findings in children and adults with bronchial asthma [1–9]. There has been much discussion of whether GOR has a negative influence as an inducer and trigger of asthma or whether it is merely a co-finding in asthma [9–10]. Studies in which asthma symptoms have been alleviated by medical [11–15] or surgical [16–20] treatment of GOR support the idea of a cause and effect relationship between GOR and asthma.

The aim of the present investigation was to see whether reflux of gastric acid was important for asthma, especially for nocturnal and morning asthma symptoms, in an unselected group of children and adolescents with bronchial asthma and pathological GOR. Therefore, we studied the reduction in gastric acid reflux by treatment with the H₂-blocker ranitidine, taken as a single dose in the evening during four weeks, to see whether it could improve asthma symptoms and lung function. We thought that a reduction of nocturnal or morning asthma symptoms by at least 50% would indicate that acid reflux is of major importance for asthma. Asthmatic subjects with normal GOR served as controls, should there be a beneficial or negative effect of ranitidine on asthma not related to its effect on gastric acid reflux.
or taking antacids; and grade III disabling symptoms (table 1). Nocturnal and morning asthma was graded I–IV. Grade I denoted no asthma attacks in the night or in the morning; grade II denoted asthma attacks 1–9 nights or mornings; grade III denoted asthma attacks 10–99 nights or mornings, and grade IV denoted asthma attacks during ≥100 nights or mornings over the previous year.

<table>
<thead>
<tr>
<th>Table 1. – Demographic data, percentage total reflux time, number of patients with positive acid perfusion test (APT), oesophageal symptoms, asthma history, and asthma medication in the patients with normal and those with pathological GOR</th>
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</thead>
<tbody>
<tr>
<td>Normal GOR n=19</td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Age yrs, mean (range)</td>
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<td>Asthma duration yrs, mean (range)</td>
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<td>Reflux time %, mean±SEM</td>
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<tr>
<td>Positive APT n</td>
</tr>
<tr>
<td>Heartburn grade n</td>
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<tr>
<td>Regurgitation grade n</td>
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<tr>
<td>Dysphagia grade n</td>
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<tr>
<td>Nocturnal/morning asthma grade n</td>
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<td>Medication n</td>
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<tr>
<td>Sodium cromoglycate</td>
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<td>Inhaled steroids</td>
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<td>Oral β2-agonists</td>
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<td>Oral theophylline</td>
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<td>Oral steroids</td>
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GOR: gastro-oesophageal reflux; n: number of patients.

Eighteen of the 37 subjects (49%) had pathological reflux according to the 24 h pH test, i.e. reflux to the distal oesophagus during more than 1% of the recording period [22], and 13 subjects (35%) had a positive APT, i.e. heartburn or chest pain during acid infusion, at the pretrial oesophageal investigation [8].

The study was arranged as a randomized, double-blind, cross-over trial with a two week run-in period before the first four week treatment period and a two week wash-out period before the second treatment period. Patients with a body weight (B.W.) <40 kg were supplied with 28 tablets before each treatment period, each containing 150 mg ranitidine or placebo, respectively. These patients were instructed to take two tablets in the evening, one hour before going to bed, during the treatment periods. The patients with a B.W. <40 kg were given 4.30 mg (mean; range 3.85–5.00 mg) ranitidine·kg⁻¹ B.W. per day and the heavier subjects were given 5.63 mg tablets before each treatment period, each containing 150 mg ranitidine or placebo, respectively. These patients were instructed to take two tablets in the evening, one hour before going to bed, during the treatment periods.

The main evaluation of the trial was based on daily record cards. The patients were instructed to record asthma symptoms and peak expiratory flow rate (PEFR), using a Wright mini peak flow meter twice daily. Each morning the patients made separate notes on any asthma symptoms, which had appeared during the previous night and the morning hours, and performed three PEFR recordings before medication, the highest of these three values being registered. In the evening they made a note of the degree of wheezing, coughing, and restriction in activities that had occurred during the day. They were also instructed to perform three PEFR recordings and to note the highest of the three. All symptoms were graded from 0 to 3 points. Zero denoted no symptoms at all and
3 points indicated very severe symptoms. The maximum daily asthma symptom score was 15.

All medication taken during the day was recorded. The patients were told to note possible adverse reactions to the treatment in their record cards.

The patients were seen at the clinic by one doctor (PMG) on three occasions: i.e. on the day after completion of the run-in period, and on the day after completion of each of the two treatment periods. On these occasions spirometry (forced expiratory volume in one second (FEV₁)) was performed with a dry sealed spirometer (Vicatest 5®, Mijnhardt, The Netherlands), as well as a bronchial histamine challenge. Before evaluation of data, FEV₁ and PEFR were transformed into percentage of the predicted values [23].

The histamine challenge was performed if the FEV₁ was >70% of the predicted FEV₁ values [23]. The same jet nebulizer (Pari Boy®, Paul Ritzau Pari-Werk GmbH, FRG) was used throughout the trial. After checking that the FEV₁ was stable within 5%, the patients inhaled saline for 2 min and the FEV₁, recorded after saline was used as baseline. Histamine chloride solutions were then inhaled by 2 min tidal volume breathing at 5 min intervals, starting with a concentration of 0.03 mg·ml⁻¹ and increasing by fourfold increments up to 8 mg·ml⁻¹ or until a fall in FEV₁ by at least 20% was recorded. The provoking concentration of histamine causing a 20% fall in FEV₁ (PC₂₀₅) was calculated by logarithmic interpolation.

At the three visits to the clinic the asthma symptoms and oesophageal symptoms over the previous week were evaluated by means of a Visual Analogue Scale (VAS). Symptoms were scored on a VAS ranging from 0-10 cm, with 1 cm marks between the endpoints. At the last visit to the clinic the patients were asked which treatment period they had preferred as regards their asthma symptoms.

Venous blood samples for blood cell count, serum concentrations of electrolytes, creatinine, urea, bilirubin, liver transaminases, alkaline phosphatases, and a urinary dip stick, were taken at each visit to the clinic.

**Statistical analysis**

The trial was dimensioned with an aim of obtaining a 90% chance of detecting a 50% reduction of nocturnal and morning asthma symptoms. The Wilcoxon's signed rank test was used for comparison of the placebo and the ranitidine treatment periods separately in the patients with and in those without pathological GOR. A comparison between the two groups of patients, regarding the effect of ranitidine on asthma, i.e. the difference in asthma symptom score between the ranitidine and placebo periods, was further performed and analysed by the Mann-Whitney U-test. A p-value <0.05 was regarded as significant. Two-tailed tests were used throughout. Regression analysis was used to see if the difference in asthma symptoms between the ranitidine and placebo periods correlated with percentage reflux time at the previous oesophageal pH monitoring.

**Ethics**

The study was approved by the Ethics Committee for Human Research at the University Hospital of Linköping and written consent was obtained from all subjects and their parents.

**Results**

Comparison between the complete four week ranitidine and the placebo period showed no significant reduction of asthma symptoms or improvement of morning or evening PEFR during ranitidine treatment in either the patients with pathological or in those with normal GOR. The patients with pathological acid reflux had a beneficial effect on nocturnal asthma symptoms significantly more often (fig. 1) than those with normal reflux. The regression analysis showed significant positive correlations between the total percentage reflux time at pH monitoring and the reduction of nocturnal asthma symptom score (r=0.46; d.f.=35; p<0.01), nocturnal-morning asthma symptoms by the VAS (r=0.39; p<0.05) (fig. 2), and total asthma symptom score (r=0.35; p<0.05) (fig. 3) during ranitidine treatment.

![Fig. 1. - Nocturnal asthma symptom score during the placebo and the ranitidine treatment periods, and the difference in score between the two periods, in the patients with pathological and in those with normal gastro-oesophageal reflux (GOR). Means and SEM are given. Statistical comparison between the placebo and the ranitidine periods was performed separately for the two groups of patients by the Wilcoxon's signed rank test. The effect of treatment (ranitidine-placebo score) was compared between the two groups by the Mann-Whitney U-test. ± : placebo; ZZ: ranitidine; n=18 n=19](image)
measurements after both treatment periods were restricted to 12 of the 19 patients with normal GOR, and to 10 of the 18 patients with pathological reflux. No significant change in bronchial histamine reactivity was seen between the two test occasions in either patient group (table 2). The ranitidine period was not preferred significantly more often than the placebo period in either group (table 2).

The VAS disclosed only mild and infrequent oesophageal symptoms in both groups during the placebo period and there was no significant difference between the two periods in either group of patients.

Three subjects reported mild side-effects during the ranitidine period, one with irregular and loose stools, the second one had abdominal pain twice during the first days of treatment, and the third complained of morning fatigue more than usual. Five subjects reported possible side-effects during the placebo period: one complained of hoarseness, the second one had slight tremor initially, the third one developed urticaria, the fourth had epigastric pain on a few occasions and the fifth patient had a slight headache during the first days of treatment.

No systematic or individual changes in the blood biochemistry or urinary tests were seen between the three test occasions. One patient had high serum creatinine (110 μmol·L⁻¹; reference value: 40–100 μmol·L⁻¹), on all three occasions. She had normal urinary dip stick findings and a normal blood pressure. At follow-up, a radiological examination of the kidneys was performed showing small kidneys, possibly due to previous pyelonephritis.

This study in children and adolescents with bronchial asthma shows that an oral dose of ranitidine taken in the evening, in addition to ordinary asthma medication, produced a statistically significant, but very modest reduction (30%) of nocturnal asthma symptoms in patients with pathological GOR when compared to those with normal GOR. Regression analysis disclosed significant positive correlations.
between the improvement of nocturnal, morning and total asthma symptoms and the degree of pathological GOR at oesophageal pH monitoring. No beneficial effect of ranitidine was seen on morning or evening PEFR, PEV<sub>1</sub> or bronchial histamine reactivity.

A positive APT did not predict a positive response to ranitidine, suggesting that the effect of ranitidine treatment on asthma was more closely related to the degree of acid reflux, than to the finding of acid sensitivity of the oesophagus.

Three controlled studies on the effects of H<sub>2</sub>-blockers on asthma symptoms in adult patients with bronchial asthma and pathological GOR have previously been published [3, 12, 15], but there is no controlled study of the effect on asthma by reduction of gastric acid reflux by H<sub>2</sub>-blocker therapy in asthmatic children with GOR.

Nagel et al. [3] treated 15 adult asthmatics with pathological GOR with ranitidine 300 mg in the morning and 150 mg in the evening for seven days in a placebo-controlled study. No improvement of asthma symptoms or PEFR was seen, which might be due to the very short duration of that trial. In the study by Goodall et al. [12] 18 adults with bronchial asthma and symptoms of pathological GOR were evaluated in a double-blind, cross-over trial over six weeks with cimetidine 200 mg three times daily and 400 mg at night. A significant reduction in reflux symptoms, and nocturnal asthma symptom scores, and a minor increase in the last PEFR reading during the day, were found during the cimetidine period. In the study by Exström et al. [15], 48 adult asthmatics with symptoms of reflux were given ranitidine 150 mg twice daily and placebo, respectively, in a double-blind, cross-over fashion, over a four week period. A significant reduction in reflux symptoms and in nocturnal asthma scores was seen during the ranitidine period.

However, the positive results were confined to a subgroup of 27 patients with a history of reflux symptoms preceding episodes of asthma symptoms [15].

One explanation for the limited effect of gastric acid secretion inhibition on asthma in the present study could be that ranitidine did not sufficiently inhibit acid secretion and consequently did not reduce acid reflux enough. We gave the patients 300/150 mg ranitidine as a single evening dose as it had been shown previously that cimetidine 400 mg three times daily and 800 mg at night were insufficient to completely abolish acid reflux. The present trial indicates that reduction of acid reflux by H<sub>2</sub>-blocker therapy in asthmatic children with GOR may, thus, have a beneficial effect on asthma from H<sub>2</sub>-receptor blockade on mediator cells and bronchial smooth muscle.

The present trial indicates that reduction of acid reflux may improve asthma symptoms, but the study is not large enough to give a firm understanding of the size of treatment effects. We have in fact detected a reduction in nocturnal asthma symptoms that was supposedly obtained by a reduction in acid reflux. The size of the reduction in nocturnal asthma symptoms is estimated to be approximately 30%. However, judging from a 90% confidence interval, the true percentage reduction can be practically null in one extreme and beyond 60% in the other. Thus, the size of the effect and its clinical significance are not effectively determined in this study.

In summary, the H<sub>2</sub>-blocker ranitidine, taken as a single evening dose over a four week period by asthmatic children and adolescents, produced a small reduction in nocturnal asthma symptoms. There was a significant correlation between the improvement in asthma symptoms and the degree of acid reflux. The modest improvement during ranitidine treatment suggests that mild or moderately severe pathological acid reflux, which is often seen in children and adolescents with asthma, is not of major importance in asthma. The small size of the present study and the inability of H<sub>2</sub>-blockers to completely abolish acid reflux, however, preclude conclusive statements on the importance of pathological GOR for childhood and adolescent asthma. Therefore, further studies with more potent inhibitors of gastric acid secretion and acid reflux, such as omeprazole, are suggested.

References


