Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole

ABSTRACT: Gastro-oesophageal reflux (GOR) is an important cause of chronic cough. There has been a lack of placebo-controlled trials treating GOR related chronic cough with antireflux therapy. The aim of this study was to determine the efficacy of omeprazole on GOR related chronic cough.

After excluding other common causes of cough, oesophageal pH monitoring was performed on 48 patients with chronic cough. Twenty-nine patients found to have GOR were randomized in a double-blind fashion to receive omeprazole 40 mg o.d. or placebo for 8 weeks. After a 2-week washout period, patients were crossed over to the other treatment. Symptoms were recorded daily in a diary.

Twenty-one patients completed both treatment periods. Cough (p = 0.02) and gastric symptoms (p = 0.003) improved significantly during the omeprazole treatment in twelve patients who received placebo during the first and omeprazole during the second 8-week period. In nine patients who received omeprazole during the first 8-week period, amelioration in cough reached statistical significance only after cessation of omeprazole. Gastric symptoms also remained minor during placebo in these nine patients.

Omeprazole 40 mg o.d. seems to improve chronic cough in patients with gastro-oesophageal reflux and the effect of omeprazole in ameliorating both cough and reflux symptoms continues after treatment ceases.


*Dept of Pulmonary Diseases and **Dept of Clinical Physiology, Turku University Central Hospital, Finland.

Correspondence: T. Kiljander
Dept of Pulmonary Diseases
Turku University Central Hospital 21540 Preitilä
Finland
Fax: 358 22614300

Keywords: Chronic cough gastro-oesophageal reflux omeprazole

Received: February 2 2000
Accepted after revision June 4 2000

This study was supported financially by The Research Foundation of Pulmonary Diseases and Turku University Foundation.

Using the diagnostic protocol described by IRWIN et al. [1] in 1981, it has been shown that the four most common causes of chronic cough are: post nasal drip syndrome (PNDS), bronchial asthma, gastro-oesophageal reflux (GOR) and chronic bronchitis. These four conditions are responsible for chronic cough in ~90% of cases [2, 3]. GOR has been found to cause 10–40% of chronic cough [1–5] which may be the only manifestation of otherwise asymptomatic GOR [2, 3, 6–8].

Two mechanisms by which GOR can cause cough have been proposed: hypopharyngeal reflux and even aspiration of oesophageal contents [9–10], and acid in the distal oesophagus stimulating the oesophageal-tracheobronchial cough reflex [7, 11, 12]. There is also evidence that cough might promote GOR [13], probably by increasing the pressure gradient between the thorax and the abdomen or by causing transient lower oesophageal sphincter relaxation [8, 11]. In fact, the presence of a cough-reflux self-perpetuating cycle has been proposed [8, 11].

Many studies have shown relief in chronic cough after antireflux treatment in patients with GOR [1–7, 10, 14–19] but most were not placebo-controlled [1–7, 10, 14–15] or were retrospective [16, 17]. There have been only two placebo-controlled studies on treating GOR related chronic cough with antireflux therapy [18, 19]. However, one of these studies did not statistically compare placebo and omeprazole groups and the majority of "responders" were found during open uncontrolled omeprazole treatment after the placebo control [19], and the second has been published only in abstract form [18]. With H2-blockers, treatment periods ranging from 2 weeks to 6 months have been required before GOR related cough has been relieved [2, 18]. There is evidence that two months treatment with omeprazole is sufficient to reduce cough in patients with GOR [16].

The aim of this study was, in a randomized, double-blind, placebo-controlled manner, to evaluate the effect of omeprazole 40 mg o.d. for 8 weeks on chronic cough in patients with GOR, which was suspected to be the cause of the cough.

Materials and methods

Patients

Between October 1995 and October 1997, patients with chronic persistent cough for two months or longer [17, 20] who attended the pulmonary outpatient clinic of the Turku University Central Hospital were considered for inclusion in the study. In addition to taking a medical history and performing a full physical examination, sinus and chest radiographs and methacholine inhalation challenge were performed on all patients.

If patients had rhinitis, signs of sinusitis on sinus radiography or if physical examination revealed increased mucopurulent secretions or predominant cobblestone...
Methods

A scoring method previously used in a similar reflux asthma study was used [22]. The following symptoms were recorded daily in a diary on a scale of 0 (no symptoms) to 3 (severe symptoms): cough, heartburn, regurgitation, chest pain, and cough disturbing sleep. Afterwards, the weekly cough and night-time cough scores (both 0–21) and gastric (heartburn+regurgitation+cough disturbing sleep) symptom score (0–63) were calculated by summing the daily scores.

Patients were considered to be free of typical GOR-symptoms if they had heartburn, regurgitation, chest pain and dysphagia less than once a week.

pH-Recordings were made using semidisposable pH catheters with 15 cm between the two monocrystalline antimony electrodes (Synectics Medical, Stockholm, Sweden). pH-Catheter also had a built-in water perfused channel for manometric identification of the lower oesophageal sphincter. pH-Electrodes were calibrated in buffer solutions before each procedure.

There were no H2 blocker, prokinetic or proton pump inhibitor users in the study population. Three patients used antacids and they were asked to stop the medication for 3 days before pH monitoring and also to avoid these drugs completely during the monitoring. Otherwise patients carried on their daily routines.

A pH-probe was passed transnasally into the stomach then slowly withdrawn, and a distal pH-electrode was positioned 5 cm and proximal 20 cm above the lower oesophageal sphincter, as determined by the change in pH between the stomach and the oesophagus [23]. In 27 (56%) patients the location of the sphincter was also confirmed manometrically. An external reference electrode was attached to the skin of the chest wall, pH was recorded at 4 s intervals using a portable Digitrapper Mk III (Synectics Medical, Stockholm, Sweden). The parameters measured were those described by Johnson and DeMeester [24]. After the ambulatory recording, the data were downloaded onto an IBM compatible computer, using appropriate analysis software (Esophrogram; Gas trosoft; Irving, TX, USA). pH-Monitoring was considered to be abnormal if total time pH <4 was over 4.5% or the DeMeester score was over 14.7 [25].

Statistical analysis

The study design was a crossover study with two periods and two treatments. When comparing diary information, the average scores for the last three weeks of both treatment periods were used. Since the outcome variables were not normally distributed, nonparametric methods were applied, and the data expressed as medians (25–75% quartiles). Before testing the treatment effect, any carry-over effect was assessed using the Mann-Whitney U test taking 0.10 as a significant level [26]. Because a carry-over effect was found, the original crossover design was not used in the analysis. Instead, comparisons of measurements made at baseline and at the end of both treatment periods were performed separately among: 1) the group of patients who received placebo during the first, and omeprazole during the second, 8-week treatment period; and 2) among the patients who received omeprazole during the first, and placebo during the second, 8-week period. These pairwise comparisons were conducted using Wilcoxon’s signed-rank test, with other tests used as indicated. SAS statistical software release 6.12 (SAS Institute; Cary, NC, USA) was used in the analyses. P-values <0.05 were interpreted as statistically significant.
Results

Twenty-nine (60%) of the patients had pathological gastro-oesophageal reflux in the pH-recording and were randomized. Eight (28%) of these patients had no typical reflux symptoms. Comparison of the patients who had pathological reflux with those who did not is shown in table 1. Eight patients wanted to discontinue the intervention. Thus, 21 patients completed both treatment periods. None of these patients had to be excluded from the final analysis because of poor compliance with trial medication. Six (29%) of the patients were male and 15 (71%) female, mean (range) age was 50 (20–74) yrs and BMI 26.8 (20.7–39.9) kg m². In nine patients cough had lasted more than a year.

Because of the statistically significant carry-over effect after the wash-out period in cough (p=0.05) and night-time cough (p=0.05) scores, the original cross-over design was not used in the analyses.

In 12 patients who received placebo during the first and omeprazole during the second 8-week period (fig. 2, table 2), there was a statistically significant improvement in the cough score during omeprazole treatment compared to baseline (p=0.04) and to the end of the placebo period (p=0.02). Also, the gastric symptoms ameliorated statistically significantly during the omeprazole period compared to baseline (p=0.002) and to the end of the placebo period (p=0.003). For night-time cough, the improvement with omeprazole was not statistically significant compared to baseline (p=0.90) nor to the end of the placebo period (p=0.59).

In nine patients who received omeprazole during the first and placebo during the second 8-week period, the symptoms continued to improve after the cessation of omeprazole (fig. 3, table 3). Omeprazole decreased the median cough score from 12.0–7.7. This change was not statistically significant (p=0.13). Gastric symptoms also improved whilst taking omeprazole but this improvement was not statistically significant (p=0.34). However, symptoms continued to be relieved on placebo; day-time cough improved significantly compared to the baseline (p=0.01) and to the end of the omeprazole period (p=0.03).

Discussion

Omeprazole 40 mg o.d. for 8 weeks seems to relieve GOR-related chronic cough and the effect of omeprazole in decreasing cough, and even reflux symptoms, seems to continue after the drug is discontinued.

Among those patients who received placebo first and omeprazole second, cough improved significantly during the 8-week omeprazole therapy compared to the baseline and to the end of the placebo period. This is in accordance with several previously published studies [1–7, 10, 14–19] in which GOR-related chronic cough was relieved with medical antireflux therapy. Unfortunately most of these

Table 1. – Comparison of patients with and without pathological gastro-oesophageal reflux (GOR) during ambulatory oesophageal pH-monitoring.

<table>
<thead>
<tr>
<th></th>
<th>GOR+</th>
<th>GOR-</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>29</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age yrs</td>
<td>49 (20–74)</td>
<td>46 (29–71)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>10/19</td>
<td>4/15</td>
<td></td>
</tr>
<tr>
<td>BMI kg m²</td>
<td>26.6 (24.2–29.0)</td>
<td>24.3 (22.3–28.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mostly nocturnal cough *</td>
<td>6 (21)</td>
<td>4 (21)</td>
<td>NS*</td>
</tr>
<tr>
<td>Percentage Time with pH &lt;4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distally</td>
<td>7.5 (4.9–13.1)</td>
<td>1.9 (1.1–2.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proximally</td>
<td>2.0 (1.0–3.8)</td>
<td>0.4 (0.3–1.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percentage Time with pH &lt;4 supine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distally</td>
<td>2.1 (0.9–9.7)</td>
<td>0.2 (0.0–0.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proximally</td>
<td>0.3 (0.0–0.9)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Percentage Time with pH &lt;4 upright</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distally</td>
<td>11.2 (6.8–17.1)</td>
<td>2.7 (1.3–3.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proximally</td>
<td>2.4 (1.3–5.3)</td>
<td>0.8 (0.5–1.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>DeMeester score</td>
<td>33.0 (19.1–42.1)</td>
<td>6.7 (2.0–9.4)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data expressed as medians (25–75% quartiles), unless otherwise stated. Mann-Whitney U-test was used unless otherwise stated. BMI: body mass index; *: mean (range); *: n(%); *: data analysed by chi-squared test; NS: nonsignificant.
studies have not been placebo controlled [1–7, 10, 14, 15] or they have been retrospective [16, 17]. There is also evidence that operative treatment of GOR will improve chronic cough [27, 28].

In the group of patients who received omeprazole first and placebo second median cough score improved from 12.0–7.7 with omeprazole. Surprisingly, cough continued to be relieved during the placebo period and in fact the improvement in cough reached statistical significance only at the end of the placebo period. It is also of interest that the gastric symptoms remained minor whilst on placebo in these patients. The explanation for the lack of significant improvement in cough during omeprazole treatment in these patients is that there were two whose cough worsened whilst on omeprazole and seven whose cough was relieved by omeprazole. Although it is widely accepted that GOR causes cough [1–7] there is also evidence that cough may promote GOR [8, 11, 13]. It has been proposed that a positive feedback cycle between cough and GOR might exist [8, 11]. Lack of symptoms in these patients when on placebo might be explained by omeprazole-induced suppression of such a cough-reflux self-perpetuating cycle. Presumably due to diminished acid reflux while taking omeprazole, cough also continued to improve during the placebo phase, resulting in the carry-over effect.

With regard to the carry-over effect the present results are similar to those of Ing et al. [18]. In their crossover study with 24 patients, ranitidine 150 mg twice a day for two weeks, significantly relieved cough when compared to baseline. However, because of a carry-over effect in the patients who received ranitidine first, there was no difference between the placebo and ranitidine periods when all the patients were considered. In that study, ambulatory oesophageal pH monitoring was performed on seven patients 4–6 weeks after the ranitidine was discontinued. Significantly less GOR was found than prior to the ranitidine treatment. The investigators concluded that in patients with GOR-related cough the effect of ranitidine decreasing cough and reflux continues after administration of the drug has stopped.

In the present study GOR was found in 29 (60%) of the patients. In eight (28%) of the cases patients had no typical symptoms of GOR. This is in accordance with previous studies, which have shown that in 10–75% of cases chronic cough is the sole presenting manifestation of otherwise asymptomatic GOR [2, 3, 6–8].

It has been shown that PNDs, asthma, GOR and chronic bronchitis are responsible for chronic cough in ~90% of cases [2, 3]. After excluding other common causes of chronic cough one might have expected an even higher than 60% prevalence of GOR in the present study. There are several possible explanations why this was not found. Firstly, as the present study was not designed to investigate the causes of chronic cough the "post-treatment diagnostic criteria" of the anatomic diagnostic protocol (i.e. cough goes away after specific therapy aimed at its cause) was not utilized at the inclusion. Secondly, it has been shown that GOR can be the cause of chronic cough even when the conventional variables in the pH monitoring are normal, if the cough is associated with a reflux episode [6]. Since we wanted to be certain that all the patients who were randomized really had GOR, these traditional variables were used to classify the patients. Thus, it is possible that among those who were not considered to have GOR in this study, some may still have had reflux as the cause for their cough. It is also possible that among those not found to have GOR were some patients with psychogenic cough, a phenomenon also known to be quite common [29].

The authors accept that there are some limitations in this study. Firstly, no attention was paid to the possible multiple causes of cough. However, after excluding other common causes of chronic cough there were few (if any) patients with multiple causes for their cough among those randomized. Secondly, the exclusion criterion for PNDs was a clinical diagnosis, which can be difficult. A third point of criticism might be that the presence of a carry-over effect prevented analyses of the results in accordance with the original study design. However, the presence of the carry-over effect is interpreted as an important result rather than a limitation as discussed above. Finally, omeprazole 40 mg o.d. may not be sufficient to inhibit acid reflux in all

---

Table 2. Median (25–75% quartiles) cough and night-time cough scores (range 0–21) and gastric symptom scores (regurgitation + heartburn + chest pain) (0–63) at baseline and the end of each treatment period (average of last three weeks) in the 12 patients who received placebo first and omeprazole second.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough score</td>
<td>8.0 (7.0–11.5)</td>
<td>8.7 (7.2–13.2)</td>
<td>6.5 (2.3–10.7)**</td>
</tr>
<tr>
<td>Gastric symptom score</td>
<td>8.0 (3.0–21.0)</td>
<td>6.3 (5.0–17.3)</td>
<td>0.0 (0.0–3.0)**</td>
</tr>
<tr>
<td>Night-time cough score</td>
<td>1.5 (0.0–5.0)</td>
<td>1.7 (0.0–7.0)</td>
<td>0.3 (0.0–7.2)</td>
</tr>
</tbody>
</table>

**: Statistically significant (p < 0.05) compared to the baseline and to the end of the placebo period. Wilcoxon’s signed-rank test was used.

---

Fig. 3. – Cough scores (0–21) of individual patients at baseline and at the end of each treatment period (average of the last three weeks) in the nine patients who received omeprazole first and placebo second.
patients with GOR. However, it has been shown that omeprazole 20 mg o.d. is sufficient to effectively stop acid reflux in 73% of asthmatics with GOR, while omeprazole 40 mg/day \(^1\) was effective in 93% of patients [30]. It is likely that gastric symptoms were not significantly relieved during the omeprazole treatment among the other subgroup of patients because of their low baseline symptom score (2/63) rather than an insufficient dose of omeprazole.

To conclude, gastro-oesophageal reflux-related chronic cough seems to be relieved after 8 weeks of treatment with omeprazole, and the effect of omeprazole in decreasing cough and even reflux symptoms continues after administration of the drug has ceased, supporting the presence of a cough-reflux self-perpetuating cycle. Since the effect of antireflux treatment seems to continue after the cessation of the drug, further studies should be of parallel rather than crossover design.

**Acknowledgements.** The authors wish to thank H. Helenius, and M. Sillala for their assistance with the statistical analysis.

**References**


Table 3. – Median (25–75% quartiles) of cough and night-time cough scores (range 0–21) and gastric symptom scores (regurgitation+heartburn+chest pain) (0–63) at baseline and the end of each treatment period (average of last three weeks) in the nine patients who received omeprazole first and placebo second.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Omeprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough score</td>
<td>12.0 (7.0–14.0)</td>
<td>7.7 (4.7–10.7)</td>
<td>5.7 (1.3–7.0)**</td>
</tr>
<tr>
<td>Gastric symptom score</td>
<td>2.0 (1.0–11.0)</td>
<td>2.0 (0.0–3.7)</td>
<td>1.3 (0.0–4.0)</td>
</tr>
<tr>
<td>Night-time cough score</td>
<td>3.0 (2.0–4.0)</td>
<td>4.0 (0.3–5.0)</td>
<td>0.7 (0.0–3.7)</td>
</tr>
</tbody>
</table>

**:** Statistically significant (p<0.05) compared to the baseline and to the end of the omeprazole period. Wilcoxon’s signed-rank test was used.


