

No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a)symptomatic gastro-oesophageal reflux

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ABSTRACT: Acid gastro-oesophageal reflux may aggravate respiratory symptoms in patients with asthma and chronic obstructive pulmonary disease (COPD) by increasing airway hyperresponsiveness through vagally-mediated pathways. We wanted to determine whether elimination of acid reflux could improve symptoms in such patients.

In a randomized, double-blind, placebo-controlled study, 36 allergic and nonallergic subjects (17 males and 19 females, mean age 52 yrs), with airway obstruction and severe airway hyperresponsiveness despite maintenance treatment with an inhaled corticosteroid and with increased acid gastro-oesophageal reflux, were treated either with omeprazole, 40 mg *b.i.d.*, or placebo for 3 months. Primary endpoints were: airway hyperresponsiveness, as determined by the provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second (PC₂₀); and airway obstruction. Secondary endpoints were: peak expiratory flow variability; reversibility to inhaled ipratropium bromide as a parameter of vagal activity; asthma symptoms scores; and medication used. Reflux was measured by 24 h ambulatory intraoesophageal pH measurement.

Omeprazole, 40 mg *b.i.d.*, for 3 months had no beneficial effect on any of the pulmonary parameters, despite its profound effect on acid reflux and improvement of reflux symptoms scores, compared to placebo.

The results of this study do not support a role for intensive antireflux therapy to improve pulmonary symptoms and function in patients with asthma and chronic obstructive pulmonary disease, who have severe airway hyperresponsiveness despite maintenance treatment with inhaled corticosteroids.

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Many patients with asthma and chronic obstructive pulmonary disease (COPD) are frequently affected by an increase in symptoms and airways obstruction. Several triggers can exacerbate the disease by eliciting smooth muscle contraction, airway inflammation, airway wall oedema and hypersecretion of mucus. One such factor may be gastro-oesophageal reflux (GER). The incidence of GER among asthmatics exceeds that of the general population, reportedly ranging 40–80% [1–3], thereby constituting a possibly important factor for the instability of the disease. Potential mechanisms underlying GER-induced airway symptomatology are thought to be microaspiration of acid into the airways with subsequent induction of an inflammatory response and bronchoconstriction, or stimulation of acid sensitive receptors in the oesophageal wall. The latter may either cause bronchoconstriction mediated by a direct vagal reflex or increase airway hyperresponsiveness through vagally-mediated pathways [3–8].

Short-term experiments exploring the above mechanisms have focused on microaspiration and a direct vagal reflex. These studies have shown conflicting results. The

same is true for long-term studies. Some studies have indicated that pulmonary symptoms and lung function can be improved by intensive treatment of acid reflux, both by surgery and medical treatment [9–13]; however this has not been confirmed in other studies [14, 15]. The discrepancy between outcomes may result from the fact that these studies did not consider airway hyperresponsiveness as an inclusion criterion or an end parameter. This may have affected the results, since oesophageal acid perfusion may be associated with an increase in airway hyperresponsiveness [16]. Furthermore, most studies have lacked objective measurements of the effect of antireflux measures, and negative results with respect to pulmonary function may have been due to insufficient antireflux therapy.

The aim of the present study was to investigate whether patients with severe airway hyperresponsiveness despite treatment with inhaled corticosteroids would benefit from the most effective medical treatment for acid reflux, *i.e.* a proton pump inhibitor in a high dose (omeprazole, 40 mg *b.i.d.*). Subjective and objective measures of clinical pulmonary stability were assessed by recording symptoms,

peak expiratory flow (PEF), spirometry and airway hyperresponsiveness to methacholine. The effectiveness of treatment with respect to reflux was measured by 24 h registration of intraoesophageal pH.

Patients and methods

Patients

Allergic and nonallergic individuals, aged 18–80 yrs, with airway obstruction and severe airway hyperresponsiveness (*i.e.*, provocative concentration of methacholine bromide causing a $\geq 20\%$ fall in forced expiratory volume in one second (PC₂₀) of less than 2 mg·mL⁻¹), despite maintenance treatment with an inhaled corticosteroid of at least 0.4 mg·day⁻¹, were eligible for this study when there was: documented increased acid reflux (*vice infra*); and a baseline forced expiratory volume in one second (FEV₁) >1.25 L. None of the subjects had an upper and/or lower respiratory tract infection or used oral corticosteroids during the 2 months prior to the study. No participant used antireflux medication during the last month prior to the study, with the exception of antacids. Patients with other concomitant lung diseases were excluded from the study. All patients gave written informed consent and the study was approved by the hospital's Medical Ethics Committee.

Study design

The study was performed in a randomized, double-blind, placebo-controlled parallel manner. Participants were stratified for their PC₂₀, *i.e.* ≥ 0.6 and <0.6 mg·mL⁻¹. Allocation to either of the groups was performed using a computer-generated randomization list. The stratification procedure resulted in a good balance in PC₂₀ values over the omeprazole and placebo groups. Subjects received either omeprazole, 40 mg *b.i.d.*, or placebo for 12 weeks. Initial studies included a reversibility test with ipratropium bromide (40 µg), and intraoesophageal 24 h pH measurement. To investigate the possibility of a direct effect of omeprazole on hyperresponsiveness, PC₂₀ was assessed prior to the study on two separate days, 1–3 h after omeprazole 40 mg and placebo, respectively, in a double-blind, randomized fashion. Patients visited the outpatient clinic at baseline and every 4 weeks.

During the week before each visit, PEF values were recorded at home with a mini-Wright peak flow meter, and pulmonary symptoms were scored on a four point scale every morning and evening. Spirometry was performed every 4 weeks during the study. The reversibility test, intraoesophageal 24 h pH measurement, and responsiveness to methacholine were assessed again at the final visit. Compliance was assessed by counting capsules every 4 weeks.

Methods

Twenty four hour ambulatory intraoesophageal pH measurement was performed with a glass pH electrode (Ingold, Urdorf, Switzerland) 5 cm above the lower oeso-

phageal sphincter, which was localized manometrically using a solid state pressure transducer (Gaeltec Ltd, Isle of Skye, UK). Data were stored in a solid state memory device (Gastrograph Mark II; Fresenius GmbH, Oberursel, Germany), and were analysed with a computer-assisted program (analysis program Gastroware; MIC A.G., Solothurn, Switzerland) with respect to total, upright and supine time with pH <4.0. Increased GER was defined as >4% of 24 h registration with pH <4.0, or >3% during the supine position [17, 18].

Spirometry was performed using a calibrated, water-sealed spirometer (Lode BV, Groningen, the Netherlands). FEV₁ and inspiratory vital capacity (IVC) were measured until three reproducible measures (<5% difference) were obtained and the highest values were used. Reversibility of airway obstruction was tested with FEV₁ measurements before and 45 min after two single inhalations of 20 µg of ipratropium bromide (Atrovent®; Boehringer Ingelheim, Germany) from a metered-dose inhaler, administered by a volume chamber. Reversibility is expressed as the absolute increase in FEV₁ as% predicted (Δ FEV₁% pred).

A methacholine challenge test was performed with a DeVilbiss 646 Nebulizer (DeVilbiss Health Care Inc., Somerset, PA, USA) at a flow rate of 8 L·min⁻¹, calibrated to 0.12 mL·min⁻¹ output. Methacholine bromide solutions were prepared in phosphate-buffered saline (in doubling concentration 0.038–19.6 mg·mL⁻¹; Sigma Chemical Co., St Louis, MO, USA). The best of three FEV₁ attempts was taken as baseline FEV₁. Solutions were nebulized during 2 min tidal breathing at 5 min dosing intervals. FEV₁ was measured 30 and 90 s after each dose. The test was stopped when FEV₁ fell >20% from baseline or when the highest concentration was reached. PC₂₀ was calculated by interpolation of the last two points on a "log-doses" versus "% fall from baseline FEV₁" scale.

PEF was assessed with a mini-Wright peak flow meter every morning upon awakening, before taking a bronchodilator if required, and every evening at bedtime, again before any bronchodilator. The highest PEF value of three blows was recorded. PEF variability was defined as diurnal variability (evening PEF - morning PEF/mean PEF of that day $\times 100\%$) and day-to-day variability (co-efficient of variation of morning, evening and all values).

Patients scored pulmonary symptoms (dyspnoea, cough) during the day and night, according to the 0–3 scale: 0 = none; 1 = mild (awareness of symptoms and/or signs which are easily tolerated); 2 = moderate (some discomfort, *i.e.* symptoms and/or signs causing interference with daily life/sleep); 3 = severe (incapacitating, *i.e.* inability to perform usual activities or work/sleep). Similarly, the numbers and times of inhalation of bronchodilators taken during this week, were registered. Before the start of the study and at each visit, patients were asked to give an overall evaluation of their reflux symptoms if present, on a 0–3 point scale (see above). Symptoms evaluated were heartburn, regurgitation and dysphagia.

Statistical analysis

Results are presented as mean values and SD unless otherwise stated. After checking for normal distribution, differences between the treatment arms were assessed by Student's *t*-test. Analyses were performed based on all

Table 1. – Data on demography, pulmonary function and reflux of the two study groups at entry into the study

	Omeprazole group			Placebo group		
	Total	Reversible	Irreversible	Total	Reversible	Irreversible
Patients n	18	10	8	18	6	12
Age yrs	51 (10)	52 (8)	51 (12)	52 (17)	44 (18)	56 (16)
Sex M/F	8/10	5/5	3/5	9/9	2/4	7/5
Weight kg	84 (11)	84 (8)	85 (15)	75 (15)	74 (20)	77 (14)
Time pH <4 % total time	12 (11)	14 (13)	8 (4)	9 (5)	9 (7)	8 (3)
FEV ₁ % pred	66 (20)	64 (21)	69 (19)	75 (23)	68 (19)	79 (25)
FEV ₁ /VC %	58.7 (16.0)	56.0 (16.8)	62.1 (15.3)	62.0 (15.7)	61.9 (16.2)	63.2 (16.4)
Morning PEF L·min ⁻¹	329 (91)	313 (84)	349 (102)	321 (109)	359 (125)	306 (102)
ΔFEV ₁ % pred	11 (7)	14 (7)	6 (3)	9 (9)	18 (7)	4 (4)
log _e PC ₂₀ mg·mL ⁻¹	-0.81	-0.78	-0.85	-0.75	-0.90	-0.73
Geometric mean	1.48	1.75	1.18	1.41	1.31	1.57
Dysphagia*	2/1/0	2/1/0	0/0/0	3/0/0	1/0/0	2/0/0
Heartburn*	9/0/0	4/0/0	5/0/0	9/3/0	1/2/0	7/1/0
Regurgitation*	3/0/0	1/0/0	2/0/0	4/3/0	1/2/0	3/1/0

Data are expressed as mean and SD in parenthesis, unless otherwise stated. *: figures x/y/z represent numbers of patients with mild, moderate and severe complaints, respectively. M: male; F: female; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value; VC: vital capacity; PEF: peak expiratory flow; ΔFEV₁: improvement in FEV₁ after inhaling 40 µg of ipratropium bromide; PC₂₀: provocative concentration of methacholine causing a 20% fall in FEV₁; Reversible: ΔFEV₁ ≥9% pred.

Table 2. – Lung function variables at baseline and at the end of the study in the omeprazole and placebo group

	Omeprazole group			Placebo group		
	Baseline	Pts n	Week 12	Baseline	Pts n	Week 12
FEV ₁ L	2.13 (0.80)	16	2.21 (0.70)	2.20 (0.88)	14	2.23 (0.81)
ΔFEV ₁ % pred	10.7 (7.7)	15	10.3 (7.8)	10.0 (9.8)	11	6.8 (5.4)
PEF morning L·min ⁻¹	349 (83)	15	322 (109)	322 (109)	13	335 (98)
PEF variability %	4.1 (6.4)	15	3.3 (4.8)	8.1 (8.7)	13	9.1 (12.6)

Single test results not available in case n<16 (omeprazole) or <14 (placebo). Data are presented as mean, and SD in parenthesis. Pts: patients. For further definitions see legend to table 1.

patients treated. PC₂₀ methacholine values were log transformed, one unit change representing one dose step. For change in PC₂₀ during the study, PC₂₀ values after placebo pretreatment were used. For diary variables, the mean of the last 7 days before each visit were used for analyses. One-way analyses of variance (ANOVA) were used for the change in a variable between baseline and the end of the study. For reflux symptom scores, a Wilcoxon rank sum test was used with treatment as classifier.

Results

Thirty six patients were enrolled into the study, six discontinued the study (two in the omeprazole group and four in the placebo group), five because of an exacerbation and one was lost to follow-up. There were no significant differences in baseline characteristics between the two treatment groups. Table 1 shows the clinical characteristics of patients who were reversible (improvement ≥9% pred) or irreversible to inhaling 40 µg of ipratropium bromide. Compliance was low, 13 patients having taken less than 75% of the study drugs, equally divided between the two treatment arms.

Omeprazole effectively reduced acid reflux, the proportion of time with pH <4 was reduced from 12.2 (11.0) to 2.0 (3.0)%, whereas in the placebo group the proportion of time with pH <4 was 9.5 (5.1) and 7.5 (4.6)%, respectively. In addition heartburn as a reflux symptom was significantly improved with omeprazole, nine patients in the omeprazole arm being asymptomatic at Visit 1 and 16 at Visit 4, compared to six and eight in the placebo arm, respectively. There were no significant improvements in

other oesophageal symptoms, largely due to lack of symptoms at baseline (table 1).

Reversibility, FEV₁, vital capacity (VC) and PEF measurements (the latter being expressed either as absolute values in morning and evening or as diurnal or day-to-day PEF variability) were not affected by omeprazole (table 2). PC₂₀ methacholine did not change significantly after a single dose of omeprazole (fig. 1), nor after 12 weeks treatment (fig. 2). Respiratory symptoms did not significantly change apart from cough at night, overall score being 0.43 (0.65) and 0.45 (0.51) at Visits 1 and 4 with omeprazole and 0.78 (0.74) and 0.42 (0.64) with placebo, respectively.

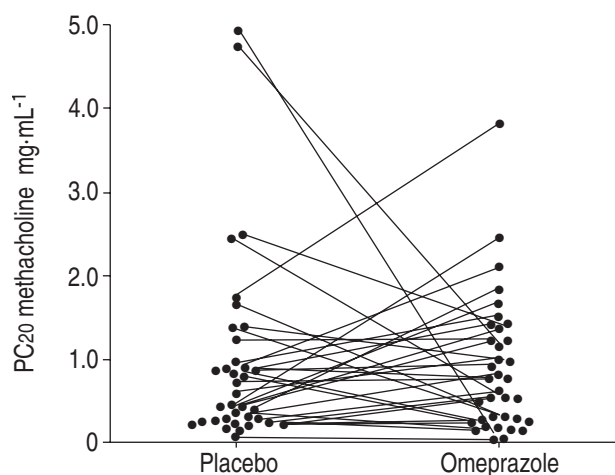


Fig. 1. – PC₂₀ methacholine 1–3 h after placebo and a single dose of omeprazole (40 mg). PC₂₀: provocative concentration producing a 20% fall in forced expiratory volume in one second.

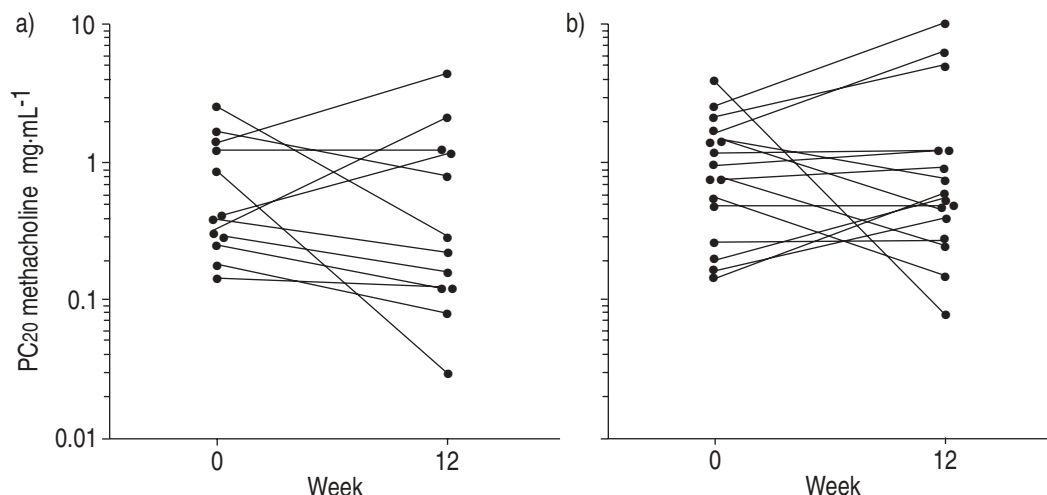


Fig. 2. — PC₂₀ methacholine before and at the end of 12 weeks of treatment with: a) placebo (data from two patients not available); and b) omeprazole (40 mg *b.i.d.*). For definitions see legend to figure 1.

Discussion

No clinical benefit of high-dose omeprazole could be established in this group of asthma and COPD patients with severe airway hyperresponsiveness and increased gastro-oesophageal acid reflux. These results are in contrast to those of some studies [9–13], but are comparable with those of others [14, 15]. The failure to show any benefit in studies has been ascribed to several factors, including insufficient inhibition of acid reflux and the short duration of the study treatment. Both of these factors were taken into account in the present study; thus, other reasons for the lack of efficacy should be sought. One such factor may be the power of the study. With the observed standard deviation of the change in \log_2 PC₂₀ from baseline (1.97), 130 patients would have been needed to reach the generally accepted meaningful difference of 1.0 doubling dose with a power of 80%. However, close inspection of the individual data did not reveal a trend towards improvement with omeprazole. The clinical relevance of a small positive effect when it is necessary to include such a large number (130) of individuals in a study is also doubtful. Finally, evaluation of only those individuals in the omeprazole group with effective management of reflux and those in the placebo group with repeatedly high reflux scores did not change the results.

Both nonallergic and allergic individuals were included in this study, whereas some authors suggest that specifically nonallergic asthmatics benefit from antireflux treatment [10, 19]. Another point of criticism could be that we did not investigate only those patients with gastro-oesophageal reflux symptoms that had started before asthma symptoms appeared. Other investigators have suggested that the latter subjects are specifically the ones in whom antireflux measures are most successful with regard to improving pulmonary symptoms [19]. However, positive results have been reported to occur in other groups as well [9, 10]. Finally, one study suggested that the effects might be better in asthmatic individuals compared with bronchitic patients [3]. Whereas all of the present patients exhibited severe airway hyperresponsiveness, only 16 of them were reversible to inhaled ipratropium bromide. However, no clinical effect was seen within the group with reversi-

ble airway obstruction either, despite adequate reduction of acid reflux by omeprazole.

As to mechanisms by which acid reflux may induce worsening of asthma symptoms, this study does not provide new insights. The fact that strong inhibition of reflux for 12 weeks does not have any appreciable effect on airway hyperresponsiveness almost precludes that any effect is mediated through such a mechanism. Nevertheless, it might be that even 12 weeks of treatment was too short a duration to obtain measurable improvement and that a similar trial for a more extended period, for example a year, might be worthwhile.

In conclusion, this study does not support screening of symptomatic patients with asthma and chronic obstructive pulmonary disease with severe airway hyperresponsiveness, despite their regular use of inhaled corticosteroids, for the presence of gastro-oesophageal reflux. Though individual cases have been described who do respond to omeprazole treatment, the present results do not suggest a general role for acid suppressive therapy in patients with asthma and chronic obstructive pulmonary disease.

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