CHRONIC COUGH AND ESOMEPRAZOLE: A DOUBLE-BLIND PLACEBO-CONTROLLED PARALLEL STUDY

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ABSTRACT

Background and objective: Gastro-oesophageal reflux has been implicated in the pathogenesis of chronic cough. Guidelines on management suggest a therapeutic trial of anti-reflux medication. Esomeprazole is a proton pump inhibitor licensed for the long-term treatment of acid reflux in adults and we compared the effects of esomeprazole and placebo on patients with chronic cough.

Methods: This was a prospective, single-centre, randomized, double-blind, placebo-controlled, parallel group study conducted over 8 weeks. Fifty adult non-smokers with chronic cough and normal spirometry were randomized. Patients completed cough-related quality-of-life and symptom questionnaires and subjective scores of cough frequency and severity at the beginning and end of the study. They also kept a daily diary of symptom scores. Citric acid cough challenge and laryngoscopic examination were performed at baseline and the end of the study. The primary outcome was improvement in cough score.

Results: There were no differences in cough scores in the placebo and treatment arms of the study although some significant improvements were noted when compared to baseline. In the cough diary scores there was a trend towards greater improvement in the treatment arm in patients with dyspepsia.

Conclusions: Esomeprazole did not have a clinically important effect greater than placebo in patients with cough. It suggests a marked placebo effect in the treatment of cough.

INTRODUCTION

The classic symptoms of gastro-oesophageal reflux (GOR) have been commonly associated with chronic cough in a number of prospective studies. This has led to the hypothesis that GOR is a causal factor in the pathogenesis of chronic cough. Acid suppression with proton pump inhibitors (PPI) has become established as the first line treatment for controlling the peptic symptoms of GOR.[1] These recommendations have been extrapolated to include the extra-oesophageal manifestations of GOR and current guidelines on the management of chronic cough suggest a therapeutic trial of anti-acid medication in those patients thought to have reflux-related cough.[2,3] In patients not responding to treatment for other causes of cough, trials are again recommended to exclude 'silent' reflux.[4]

Several uncontrolled studies have reported that anti-acid therapy improves GOR-associated chronic cough. This contrasts with the much more modest improvement observed in randomized controlled trials. A recent systematic review and meta-analysis of randomized controlled trials of GOR interventions in chronic cough concluded that there was a need for further evidence to delineate the potential beneficial effect of PPI.[5]

Our objective was to evaluate the efficacy of treatment with a PPI in a prospective double-blind randomized placebo-controlled parallel group study in patients with a clinical history of the extra-oesophageal manifestations of reflux in association with chronic cough.

METHODS

Patients

Adult non-smoking patients with chronic cough of greater than 8 weeks' duration without obvious lung disease and with a normal chest radiograph were recruited from the Hull Cough Clinic. Randomized patients had clinical features consistent with reflux-related cough.[6] Common symptoms of reflux-related cough include cough on phonation or on bending in association with food and eating. The presence of heartburn or dyspepsia was not required to make the diagnosis.

Patients were excluded if they were taking angiotensin-converting enzyme inhibitors and if they had used anti-acid medications or suffered a lower respiratory tract infection in the preceding 4 weeks. Eligible subjects were asked to score the severity of their cough on a numerical response scale of 0–9 and were only included if their cough score was ≥ 3. Signed informed consent was obtained from all subjects and the study was approved by the Hull and East Riding Local Ethics Committee. Prospective power calculation based on PPI responsiveness observed in 28 patients indicated that 25 subjects per group would be sufficient to provide 80% power to detect a treatment difference of two units using a 5% two-sided test. This was consistent with the number of subjects based on our previous study demonstrating the efficacy of opiate therapy in cough suppression.[7]

Measurements

Integral response score for cough

Subjects rated their symptoms on a numerical scale from 0 (best) to 9 (worst) for severity and frequency of cough at the beginning and end of the study.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ), a validated cough-related quality-of-life instrument comprising three domains (physical, psychological, social), was completed by all the subjects. The LCQ scores range from 3 to 21 with lower scores representing a poorer quality of life.[8]

Hull Airway Reflux Questionnaire

Subjects were asked to complete the Hull Airway Reflux Questionnaire (HARQ), a validated instrument detecting the symptom complex associated with reflux-induced cough hypersensitivity. This is a 14-point self-administered questionnaire with a maximum score of 70.[9] Unlike the LCQ, the HARQ is not a quality-of-life questionnaire; rather it is a diagnostic tool to detect airway reflux and is responsive to change in these symptoms.

Reflux finding score

One investigator (A.H.M.) performed laryngoscopy on consenting patients, with appearances assessed using the reflux finding score, designed to assess the physical signs of laryngopharyngeal reflux.[10]

Spirometry

Subjects performed three forced expiratory manoeuvres from total lung capacity to residual volume. Best FEV_1 and FVC were recorded.

Citric acid cough challenge

Modified DeVilbiss 646 nebulizer (DeVilbiss Healthcare, Somerset, Pennsylvania, USA) and KoKo Digidoser (Pulmonary Data Services, Louisville, Colorado, USA) system was used as recommended in the European Respiratory Society guidelines.[11] Serial dilutions from a Molar solution were made with normal saline to reach a lowest concentration of 1.95 mmol/L. Concentrations inhaled to achieve two and five coughs were recorded.

Cough and reflux diary

Subjects were asked to record a daily diary of symptoms during the study. They were asked to rate their cough symptoms from ‘no cough’ to ‘worst cough ever’ on a scale of 0 to 9. Dyspeptic symptoms were rated on a similar scale.

Study design

Subjects were randomized to receive either esomeprazole 20 mg twice daily or matched placebo in a parallel group design. Treatment was self-administered by subjects over a period of 8 weeks. Randomization and allocation to treatment groups was performed by DHP Ltd. (Powys, UK). Both subjects and site personnel were blinded to the allocation of the medication. Enrolment commenced February 2005 with the first subject commencing treatment in September 2005. The final subject completed the trial in August 2007. The EUDRACT trial number was 2004-004748-27.

Data analysis

Results were analysed on an intention to treat basis. The primary end-point was the change in the integral cough scores. Secondary outcomes were improvements in the other measures of cough symptoms. Paired and unpaired Student's t-tests or the Wilcoxon/Mann–Whitney U-tests were used where applicable. The rate of change of the diary scores was further analysed using linear regression. SPSS statistical software (Chicago, Illinois, USA) and Microsoft Excel (Redmond, Washington, USA) were used for analysis.

RESULTS

Fifty-one patients were screened for inclusion into the study and randomized. Twenty-five patients were randomized to receive placebo and 26 esomeprazole. One patient in the treatment group was excluded after randomization due to non-disclosure of pregnancy during screening. Of the eligible patients (mean age 58.1 years) 33 were women. Overall compliance with the treatment course was good (median compliance 98.1%; range 67.5–100%). One patient was excluded from the analysis due to concomitant use of opiates. Table 1 summarizes the demographic characteristics of the study population. The two groups were well matched in terms of demographics, duration and severity of cough. There were no statistically significant differences between baseline characteristics.

Table 1. Summary of patient characteristics

Parameter	Treatment group	Placebo group
Age (mean; SD)	56.8; 12.5	59.4; 8.6
Male	8	10
Female	17	15
Cough duration in years (median; range)	2; 0.5–56	3; 0.58–20
Peptic symptoms	18	21
Never smokers	18	16
Ex-smokers	7	9

There were no serious adverse events during the study. Six subjects reported respiratory tract infection symptoms during the study period (four treatment, two placebo). One patient could not perform objective tests at follow up due to a facial injury. Enrolment and progress through the study is shown in Figure 1.

Figure 1.CONSORT diagram of participants in the study. PPI, proton pump inhibitor.

There was no significant difference in the change in integral scores for severity or frequency of cough between placebo and esomeprazole treatment (Table 2). Improvements were noted in all of the measures of cough and dyspepsia compared to baseline assessment.

Table 2. Summary of main results and between-group comparisons

Variable	Treatment group			Placebo group			Between-group P-value
	Before	After	P-value	Before	After	P-value	
Cough frequency (mean; SD)	5.8; 1.3	4.2; 2.3	0.006	5.9; 2.0	4.4; 2.7	0.006	0.92
Cough severity (mean; SD)	5.4; 1.8	3.8; 1.9	0.007	6.0; 2.0	4.3; 2.8	0.0063	0.80
LCQ score (mean; SD)	12.5; 2.6	15.1; 3.9	0.0014	12.3; 2.8	13.0; 4.7	0.053	0.25
Laryngoscopy reflux finding score (mean; SD)	7.05; 3.4	6.33; 3.4	0.82	8.2; 4.6	5.8; 4.2	0.06	0.94
HARQ score (mean; SD)	29.9; 8.9	22.6; 10.9	0.004	32.5; 12.9	25.4; 16.3	0.006	0.61
Log C2† (mean; SD)	1.88; 0.55	1.73; 0.57	0.48	1.86; 0.55	1.82; 0.69	0.64	0.66
Log C5† (mean; SD)	2.06; 0.52	2.08; 0.64	0.69	2.05; 0.56	1.96; 0.60	0.83	0.57

†Concentration of citric acid inhaled to produce two and five coughs during cough challenge testing.

HARQ, Hull Airway Reflux Questionnaire; LCQ, Leicester Cough Questionnaire.

There was no significant difference in the change in diary cough scores between the treatment group and the placebo group (Fig. 2; difference in mean reduction 0.52 in favour of the treatment group; P = 0.46). When groups were subdivided into patients exhibiting or not exhibiting symptoms of dyspepsia, the mean reduction in cough scores tended to be greater, although without statistical significance, in the treatment group in patients with dyspeptic symptoms (difference in mean reduction 0.71; P = 0.42) but not in patients without dyspeptic symptoms (−0.21; P = 0.95).

Figure 2. Mean diary cough scores during treatment period. (×) Treatment, (○) placebo, (——) linear (treatment), (- - -) linear (placebo).

There were significant improvements between baseline and end of treatment in the HARQ scores in both treatment and placebo arms. There was, however, no significant difference between the groups.

The LCQ scores showed an improvement in the treatment arm which was significant in all components of the score (overall score 12.50 vs 15.14, P < 0.002). In the placebo arm there was a trend towards improvement but only the physical component reached statistical significance (overall score 12.25 vs 13.04, P = 0.053). Again there were no significant differences between the groups.

There were no significant differences in cough challenge results before and after PPI therapy and no differences between the treatment arms. There was a slight but significant decline in spirometry results in the placebo group (mean change in FEV_1—0.08 L, P = 0.029; mean change in FVC—0.189 L, P = 0.0015). Improvements in laryngoscopy scores trended higher in the placebo group at the end of treatment but this did not reach statistical significance.

DISCUSSION

Gastro-oesophageal reflux is thought to be an aggravating factor in many patients with chronic cough.[12–14] However, the lack of consensus on diagnostic criteria of extra-oesophageal reflux makes it difficult to quantify the association. A number of uncontrolled studies have demonstrated an improvement in chronic cough with anti-acid treatment, with reports of improvement ranging from 75% to 100% of cases.[13,15,16] One study found no improvement despite effective acid suppression.[17] Randomized trials with PPI in the treatment of laryngopharyngeal reflux and posterior laryngitis, both having significant symptom overlap with reflux-associated cough, have also shown no convincing effect on cough symptoms over placebo.[18–21] A recent study using high-dose esomeprazole (40 mg bd) in patients with chronic cough without associated heart burn demonstrated, as in our study, a significant placebo response with no additional effect of esomeprazole. Unlike our study, patients were recruited from different hospital specialities and the duration of treatment was 12 weeks.[22] The similarity of the conclusion of these two separate studies strongly suggests a lack of efficacy of acid suppression as a strategy in chronic cough. In contrast, a widely quoted systematic review and meta-analysis suggested that treatment with PPI 'has some effect in some adults'.[5] However, studies included in this analysis had disparate inclusion criteria and outcome measures. The studies which recruited patients with chronic cough could be criticized for short duration of treatment, cross-over trial design and lack of a placebo control group.

Our study addresses several of the shortcomings of previous investigations. Patients were recruited based on the clinical features characteristic of GOR-associated chronic cough with exclusions limited to other known precipitants of cough. Patients were all new referrals from primary care physicians and were naïve to the specialist cough service.

The outcome measures were subjective cough scores and LCQ score which have been shown by us and others to correlate well with objectively counted cough frequency.[23,24] In this study, we suggest these subjective responses are more clinically relevant since they are routinely used to titrate treatment in practice.

Although there were significant improvements in many of the outcome measures in the treatment arm of our study, most were matched by similar improvements in the placebo group. When we analysed subgroups with and without dyspepsia, the improvement in cough diary scores was notably absent in non-dyspeptic patients although this effect failed to reach statistical significance, possibly because of subgroup sample size since our study was not powered to detect differences in the specific subgroup of patients with chronic cough and dyspeptic symptoms.

In our previous study showing morphine to be an effective treatment in chronic cough, the patients had been extensively investigated and undergone numerous therapeutic trials.[7] In that study placebo administration produced little discernible effect whereas active drug treatment produced a large and significant reduction in cough symptomatology. In contrast, in the

current study, patients were naïve to the specialist clinic and we believe the strong placebo effect demonstrated reflects this therapeutic environment. Such an effect has been frequently observed in studies of acute, chronic and experimentally induced cough in man.[25] This attribute of the cough reflex is so robust that it can be modelled in pharmacodynamic terms with a defined $T_{1/2}$.[26]

In the seminal paper published in 1955, Beecher attributed a third of the improvement in 15 clinical trials to a placebo effect.[27] Interestingly, three of these studies involved patients with cough. The placebo response varies with the nature and severity of the condition as well as outcome measure used. In studies of acute cough related to upper respiratory tract infections, 85% of the response observed can be attributed to placebo.[19] A strong placebo effect was highlighted in the meta-analysis of anti-acid therapy in chronic cough.[5] In a study of voice therapy in patients who were refractory to antitussive pharmacological treatment, a placebo intervention gave a response in one-third.[28]

The significant placebo response observed in pain therapy has been attributed to the release of endogenous opioids. This placebo response can in fact be inhibited by opioid antagonists.[29] The release of endogenous opioids could possibly explain the placebo response observed in cough as well. A 'cough model' to explain the antitussive effects of placebo has been suggested.[19]

Part of the placebo effect observed in our study could be explained by regression to the mean. Chronic cough is known to have a waxing and waning course. It is possible that, as these were all new referrals, their cough was severe and prompted the referral in the first instance. An average delay of 8 weeks between referral and consultation would however tend to mitigate this effect. As part of the selection criteria those with cough score of 2 or less were excluded from the study, again invoking regression to the mean.

The results of our study are similar to the lack of response to PPI observed in a recent large study of subjects with bronchial asthma without dyspeptic symptoms.[30] The authors erroneously concluded that the failure to demonstrate a clinically important response inferred that GOR had no role to play in severe asthma.[31] The major effect of PPI is on acid secretion. They do not alter either the frequency or duration of GOR; they simply change the pH characteristics and volume of the refluxate.[32] Impedance measurements demonstrate that non-acid reflux is responsible for many extra-oesophageal symptoms such as cough and dysphonia.[33] It is therefore unsurprising that significant improvements in cough may be difficult to demonstrate with simple acid suppression alone if chronic cough is provoked by non-acid GOR.

A criticism of our study is that it may have been too small to detect a clinically significant effect of PPI-associated suppression of coughing. The number of subjects is similar to that in our successful opiate cough suppression study and our original power calculation was based on this data.

In conclusion, a role for acid suppression in the treatment of GOR-associated chronic cough remains uncertain. Both national and international guidelines recommend trials of high intensity acid suppression as a therapeutic option. Our study suggests that the response seen may largely be due to a placebo effect. Importantly, there have been concerns regarding increased risk of developing community as well as hospital-acquired pneumonia.[34–36] Other serious potential adverse effects include the development of enteric infections such as

Clostridium difficile-associated diarrhoea and hip fractures.[37–40] PPI can also inhibit the conversion of clopidogrel to its active metabolite with a resultant loss of efficacy.[41,42]

REFERENCES

1 DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. Am. J. Gastroenterol. 1999; 94: 1434–42.

2 Irwin RS, Baumann MH, Bolser DC et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006; 129: 1S–23S.

3 Morice AH, Fontana GA, Sovijarvi AR. The diagnosis and management of chronic cough. Eur. Respir. J. 2004; 24: 481–92.

4 Pratter MR, Brightling CE, Boulet LP et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129: 222S–31S.

5 Chang AB, Lasserson TJ, Kiljander TO et al. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. Br. Med. J. 2006; 332: 11–17.

6 Everett CF, Morice AH. Clinical history in gastroesophageal cough. Respir. Med. 2007; 101: 345–8.

7 Morice AH, Menon MS, Mulrennan SA et al. Opiate therapy in chronic cough. Am. J. Respir. Crit. Care Med. 2007; 175: 312–15.

8 Birring SS, Prudon B, Carr AJ et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003; 58: 339–43.

9 Morice AH, Faruqi S, Wright CE et al. Cough hypersensitivity syndrome: a distinct clinical entity. Lung 2011; 189: 73–9.

10 Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111: 1313–17.

11 Morice AH, Fontana GA, Belvisi MG et al. ERS guidelines on the assessment of cough. Eur. Respir. J. 2007; 29: 1256–76.

12 FitzGerald JM, Allen CJ, Craven MA et al. Chronic cough and gastroesophageal reflux. CMAJ 1989; 140: 520–4.

13 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am. Rev. Respir. Dis. 1981; 123: 413–17.

14 Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and gastro-oesophageal reflux. Thorax 1991; 46: 479–83.

15 Irwin RS, Zawacki JK, Curley FJ et al. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. Am. Rev. Respir. Dis. 1989; 140: 1294–300.

16 Waring JP, Lacayo L, Hunter J et al. Chronic cough and hoarseness in patients with severe gastroesophageal reflux disease. Diagnosis and response to therapy. Dig. Dis. Sci. 1995; 40: 1093–7.

17 Irwin RS, Zawacki JK, Wilson MM et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest 2002; 121: 1132–40.

18 Wo JM, Koopman J, Harrell SP et al. Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux. Am. J. Gastroenterol. 2006; 101: 1972–8.

19 Vaezi MF, Richter JE, Stasney CR et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope 2006; 116: 254–60.

20 Noordzij JP, Khidr A, Evans BA et al. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. Laryngoscope 2001; 111: 2147–51.

21 Eherer AJ, Habermann W, Hammer HF et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. Scand. J. Gastroenterol. 2003; 38: 462–7.

22 Shaheen NJ, Crockett SD, Bright SD et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. Aliment. Pharmacol. Ther. 2011; 33: 225–34.

23 Faruqi S, Thompson R, Wright C et al. Quantifying chronic cough: objective versus subjective measurements. Respirology 2011; 16: 314–20.

24 Decalmer SC, Webster D, Kelsall AA et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax 2007; 62: 329–34.

25 Eccles R. The powerful placebo in cough studies? Pulm. Pharmacol. Ther. 2002; 15: 303–8.

26 Rostami-Hodjegan A, Abdul-Manap R, Wright CE et al. The placebo response to citric acid-induced cough: pharmacodynamics and gender differences. Pulm. Pharmacol. Ther. 2001; 14: 315–19.

27 Beecher HK. The powerful placebo. JAMA 1955; 159: 1602–6.

28 Vertigan AE, Theodoros DG, Gibson PG et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax 2006; 61: 1065–9.

29 Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc. Natl. Acad. Sci. U.S.A. 2007; 104: 11056–61.

30 Mastronarde JG, Anthonisen NR, Castro M et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. N. Engl. J. Med. 2009; 360: 1487–99.

31 Lenglinger J, Riegler M. Esomeprazole for asthma. N. Engl. J. Med. 2009; 361: 206–7.

32 Hemmink GJ, Bredenoord AJ, Weusten BL et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? Am. J. Gastroenterol. 2008; 103: 2446–53.

33 Blondeau K, Dupont LJ, Mertens V et al. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. Aliment. Pharmacol. Ther. 2007; 25: 723–32.

34 Laheij RJ, Van Ijzendoorn MC, Janssen MJ et al. Gastric acid-suppressive therapy and community-acquired respiratory infections. Aliment. Pharmacol. Ther. 2003; 18: 847–51.

35 Herzig SJ, Howell MD, Ngo LH et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009; 301: 2120–8.

36 Gulmez SE, Holm A, Frederiksen H et al. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. Arch. Intern. Med. 2007; 167: 950–5.

37 Yearsley KA, Gilby LJ, Ramadas AV et al. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. Aliment. Pharmacol. Ther. 2006; 24: 613–19.

38 Dial SJ, Delaney JA, Barkun AN et al. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA 2005; 294: 2989–95.

39 Yang YX. Proton pump inhibitor therapy and osteoporosis. Curr. Drug Saf. 2008; 3: 204–9.

40 Corley DA, Kubo A, Zhao W et al. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. Gastroenterology 2010; 139: 93–101.

41 Gilard M, Arnaud B, Cornily JC et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J. Am. Coll. Cardiol. 2008; 51: 256–60.

42 Juurlink DN, Gomes T, Ko DT et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009; 180: 713–18.