PostScript

LETTERS TO THE EDITOR

Chronic cough and gastro-oesophageal reflux

In their in-depth review of chronic cough and gastro-oesophageal reflux (GOR), Fontana and Pistolesi suggest that proton pump inhibitors are the most effective treatment for GOR related cough.[1] However, most studies evaluating the efficacy of proton pump inhibitors are not placebo controlled and do not use objective markers of cough severity to assess treatment responses. We are aware of two double blind, randomised, placebo controlled trials of proton pump inhibitors, the results of which are summarised in table 1.[2 3] These studies show no clear benefit of proton pump inhibitors in patients with chronic cough and GOR and are consistent with the negative findings of a randomised placebo controlled study of ranitidine in a similar patient population.[4] In our experience, only a small proportion of patients with chronic cough have a sustained improvement with proton pump inhibitors. Others have shown that there are no clear clinical indicators or findings on investigation that predict a treatment response.[2] Further randomised controlled trials of proton pump inhibitors are required using both objective and subjective markers of cough severity such as quality of life questionnaires,[5] cough monitors,[6] and cough reflex sensitivity[7] before we can accept that GOR is an important cause of chronic cough.

In many ways the current data in chronic cough are consistent with findings in asthma, with good evidence of a higher than expected incidence of oesophageal dysfunction and GOR[8 9] but little high quality evidence of a causal association between GOR and airway symptoms or dysfunction.[10] The interesting question is why oesophageal dysfunction occurs so commonly in patients with a diverse range of airway diseases. One possibility is that this is a manifestation of a global abnormality of upper aerodigestive reflexes,[7] perhaps due to inflammation and dysfunction of embryologically related structures. Further studies are required to investigate this possibility.

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References

1 **Fontana GA**, Pistolesi M. Cough · 3 : Chronic cough and gastro-oesophageal reflux. *Thorax* 2003;**58**:1092–5.
2 **Ours TM**, Kavuru MS, Schilz RJ, *et al*. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;**94**:3131–8.
3 **Kiljander TO**, Salomaa ER, Hietanen EK, *et al*. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;**16**:633–8.
4 **Ing AJ**, Ngu MC, Breslin AB. A randomised double-blind placebo controlled crossover study of ranitidine in patients with chronic persistent cough associated with gastroesophageal reflux. *Am Rev Respir Dis* 1992;**145**:A11.
5 **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.
6 **Matos S**, Birring SS, Patel RB, *et al*. Day time cough counts using the Leicester Cough Monitor (LCM) in patients with chronic cough and healthy controls. *Thorax* 2003;**58**:iii48.
7 **Prudon B**, Birring SS, Vara DD, *et al*. Cough and glottic stop reflex sensitivity in health and disease. *Chest* 2004 (submitted).
8 **Harding SM**, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med* 2000;**162**:34–9.
9 **Kastelik JA**, Redington AE, Aziz I, *et al*. Abnormal oesophageal motility in patients with chronic cough. *Thorax* 2003;**58**:699–702.
10 **Coughlan JL**, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. *Thorax* 2001;**56**:198–204.

Table 1 Summary of randomised, double blind, placebo controlled trials of proton pump inhibitors in patients with chronic cough and pathological GOR on 24 hour oesophageal pH studies

Study	No	Drug	Duration (months)	Improvement in cough	
				Placebo	Omeprazole
Ours *et al*[2]	17	Omeprazole 40 mg twice daily	3	0/9 (0%)	1/8 (13%)
Kiljander *et al*[3]	21	Omeprazole 40 mg/day	2	13/21 (62%)	16/21 (76%)

Authors' reply

After reading the letter by Drs Birring and Pavord concerning our review of chronic cough and gastro-oesophageal reflux (GOR),[1] it appears that there is much upon which we agree. For instance, we agree that (1) the evidence in favour of anti-acid treatment for GOR related cough is not striking; (2) we need more well designed studies to definitely assess the effectiveness of acid suppressant treatment on GOR related chronic cough; and (3) the reasons why oesophageal dysfunction is so frequent in patients with airway diseases deserve to be further investigated, and the complex interactions between the airway and the proximal gastrointestinal tract await clarification.

On the other hand, we disagree with the opinion expressed by Drs Birring and Pavord that the three randomised, placebo controlled studies[2–4] on the effectiveness of anti-acid treatment in patients with GOR related cough attained negative results, and we believe that the figures reported in their table do not satisfactorily summarise the outcomes of these studies. Notably, the studies by Kiljander *et al*[2] and Ing *et al*[3] were based on a remarkably similar experimental design. In the study by Kiljander *et al*[2] patients with GOR related cough were randomised into two treatment groups to receive either omeprazole or placebo. After a washout period, patients were then crossed over to the other treatment. The outcome measures also included the cough score. In the patients who received placebo first and omeprazole second, the cough score at the end of the omeprazole period significantly improved compared with that recorded at both baseline and the end of the placebo period; in those who received omeprazole first and placebo second, the improvement in cough score—albeit detectable at the end of the omeprazole period—reached statistical significance only after completion of the placebo period. The lack of a significant improvement in cough scores after the omeprazole period in patients who received omeprazole first was probably due, as concluded by the authors,[2] to a worsening of cough during the omeprazole period in two out of nine patients in this group. The lack of symptoms in patients during placebo treatment in those who received omeprazole first probably reflected omeprazole induced acid suppression which extended into the placebo phase resulting in a ''carryover'' effect.[4] The same phenomenon may explain the findings by Ing *et al*[3] who reported a significant fall in the cough score during ranitidine induced acid suppression compared with both baseline conditions and the placebo period when placebo was taken as the first drug, but no significant difference was found between ranitidine and placebo cough scores when ranitidine was taken as the first treatment.

Taken together, the results of the studies by Kiljander *et al*[2] and Ing *et al*,[3] rather than demonstrating the failure of anti-acid therapy, raise the question of whether the randomised, double blind, placebo controlled study design is the optimal method for evaluating the effectiveness of acid suppressant agents in the treatment of GOR related cough. The crossover trial raises the problem

of an unbiased estimate of the treatment effect when differences occur because of the different sequences in which treatments are applied. Factors that can invalidate a cross-over trial also include non-uniform pharmacological carryover effect, failure to return patients to their baseline conditions before the crossover, and non-uniform conditions of the patients over time.[4] When these problems can be anticipated, a parallel study design involving a large number of patients may be preferable.[4]

In the study by Ours *et al*,[5] six (35%) of the 17 patients with abnormal oesophageal pH monitoring studies responded to acid suppression. Thus, while the study confirms that there are patients with GOR related cough who can be successfully treated with anti-reflux therapy consisting only of acid suppression, failure of treatment in the remaining 11 patients may be due to a number of reasons such as resistance to omeprazole,[6] the presence of another undiagnosed or inadequately treated cause of cough, and the possibility that factors including (but not limited to) acid in the gastric refluxate such as pepsin and bile salts[7] may be implicated in the mediation of cough by GOR. Gastro-oesophageal dysmotility may also have a role.[8] It is to be hoped that the development of new technologies such as simultaneous monitoring of intraoesophageal impedance and pH will allow us to appreciate fully the diagnostic accuracy and reliability of 24 hour oesophageal monitoring and the role of non-acid components of refluxate in GOR related cough.

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References

1 **Fontana GA**, Pistolesi M. Cough · 3: Chronic cough and gastro-oesophageal reflux. *Thorax* 2003;**58**:1092–5.
2 **Kiljander TO**, Salomaa ERM, Hietanen EK, *et al*. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;**16**:633–8.
3 **Ing AJ**, Ngu MC, Breslin ABX. A randomised double blind placebo controlled crossover study of ranitidine in patients with chronic persistent cough (CPC) associated with gastro-oesophageal reflux (GOR). *Am Rev Respir Dis* 1992;**145**:A11.
4 **Woods JR**, Williams JG, Tavel MT. The two-period crossover design in medical research. *Ann Intern Med* 1989;**110**:560–6.
5 **Ours TM**, Kavuru MS, Schilz RJ, *et al*. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;**94**:3131–8.
6 **Leite LP**, Johnston BT, Just RJ, *et al*. Persistent acid secretion during omeprazole therapy: a study of gstric acid profiles in patients demonstrating failure of omeprazole therapy. *Am J Gastroenterol* 1996;**91**:1527–31.
7 **Ing AJ**, Ngu MC. Cough and gastro-oesophageal reflux. *Lancet* 1999;**353**:944–6.
8 **Kastelik JA**, Jackson W, Davies TW, *et al*. Measurement of gastric emptying in gastro-oesophageal reflux-related chronic cough. *Chest* 2002;**122**:2038–41.

Recruitment of ethnic minorities to asthma studies

Ethnic variations in the prevalence, severity, and management of asthma have been reported[1 2] but, apart from these recent reports, our understanding of the relationship between ethnicity and asthma is limited. This is a concern as ethnicity may be an important confounder in asthma studies through such varied influences as differences in lung function, socioeconomic disparities, and concordance with treatments.[3] Proactive ethnic trial recruitment policies exist in the US but there is no comparable legislation in Europe. We sought to investigate the hypothesis that asthma trials conducted in the US are more likely than European studies to report on the ethnicity of subjects.

Our sampling frame was the Cochrane Airways Group Trials Register which contains records of published and unpublished clinical trials. We manually searched this database for English language reports of randomised controlled trials of asthma reported during the period 2000–2. Clinical trials conducted in either the US or Europe were identified and 35 European and 35 US studies were selected using simple random sampling. Full text hard copies of all selected articles were obtained for detailed assessment of any mention of the ethnicity of study participants. A deliberately broad working definition of ''ethnicity'' was used that included any reference to race, ethnic origin, language, or nationality. On the basis of this information the studies were categorised as either detailing the ethnicity of subjects or not. One reviewer systematically extracted data on whether the ethnicity of subjects was reported using a pre-piloted data extraction form and a second reviewer independently verified a sample of extracted data. Disagreements were resolved through discussion with provision to refer to a third reviewer if necessary.

Descriptive statistics were used to determine the proportion of studies reporting information on the ethnicity of study subjects and the χ^2 test was used to compare reporting of ethnicity in European and US published trial reports. Assuming that 50% of US and 15% of European asthma trials report on the ethnicity of participants, we estimated that we would need to extract data on a total of 64 studies (32 from each area) in order to have 80% power of detecting a difference at the 5% significance level.

Overall, 23 of 70 reports (32.9%) included information on the ethnic profile of participants (table 1). US studies (n = 22) were significantly more likely to report on ethnicity than European studies (n = 1): 62.9% *v* 2.9%; RR = 22; 95% CI 3.1 to 154.4; p<0.0001. Among the European trials, 13 were UK based and the single European trial reporting ethnicity was from the UK.

Thus, recent asthma trials conducted in the US are 22 times more likely than those conducted in Europe to report information on the ethnicity of study participants. The random selection procedures adopted to identify suitable trials and the standardised extraction of data with independent verification and an ''a priori'' agreed approach to handle disagreements should, we believe, have minimised the impact of selection and/or information biases affecting these findings.

Table 1 Frequency of asthma studies reporting ethnicity of study subjects

Location of study	Ethnicity reported		Total
	Yes (%)	No (%)	
US	22 (62.9)	13 (37.2)	35
Europe	1 (2.9)	34 (97.1)	35
Total	23 (32.9)	47 (67.1)	70

$\chi^2 = 28.56$ with 1 degree of freedom; p<0.0001.

Our results seem likely to reflect proactive policies in the US. For example, all federally supported programmes with sufficient sample size are required to report statistics according to race/ethnicity.[4] Furthermore, the National Institute of Health regularly issues guidelines regarding inclusion of women and ethnic minorities into clinical trials, and less than 4% of grant applications are reported to be in breach of these guidelines.

Although the US fares better than Europe, it is still worrying that only 62.9% of recently published clinical trials from the US report on the ethnicity of participants. This finding may have several possible explanations, including difficulties in identifying, enrolling, communicating with, and following up patients from minority ethnic groups in asthma trials. Mechanisms and standards to ensure inclusion and reporting of ethnic minority communities in asthma studies are needed. These are absent in current trial reporting guidelines (CONSORT) and we suggest that, where appropriate, the merits of insisting on presentation of such data should be debated.[5] Although the Standards for Reporting of Diagnostic Accuracy (STARD) statement is a move in the right direction, this still lacks explicit requirements for the reporting of the ethnicity of study participants. In addition, European governments and respiratory bodies should consider the US model for promoting the inclusion of participants from ethnic minorities in asthma research.

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References

1 **Moudgil H**, Honeybourne D. Ethnic influences on the prevalence, morbidity and management of asthma in the United Kingdom, with particular reference to Asian communities. *Asthma J* 2000;**5**:16–21.
2 **Partridge MR**. In what way may race, ethnicity or culture influence asthma outcomes? *Thorax* 2000;**55**:175–6.
3 **Sheikh A**. *Improving asthma care for ethnic minority patients*. Warwick: NRTC, 2001.
4 **Office of Management and Budget**. *Race and ethnic standards for federal statistics and administrative reporting*, Directive no 15.http://www.whitehouse.gov/omb/fedreg/directive_15.html (accessed 17 February 2003).
5 **Revised Consort Statement**. http://www.consort-statement.org/ (accessed 25 June 2003).

Reaction to cheese during TB treatment

We describe a case of a reaction to cheese in a patient with tuberculosis (TB) while on treatment with isoniazid.

A 26 year old woman diagnosed with breast TB after isolation of drug sensitive *Mycobacterium tuberculosis* by breast nodule biopsy was started on treatment on 18 February 2003 with four drugs (rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 2 g/day, and ethambutol 1.2 g/day). On 14 April she came for the scheduled medical visit reporting episodes of facial flushing, respiratory distress (''constriction of throat''), and headache. The first episode was noticed on 30 March while dining and lasted 30 minutes. The same symptoms occurred the following day during lunch; the blood pressure measured during the episode was 110/90 (normally 85/60). A further two similar episodes occurred, one of which was not associated with eating.

The patient denied digestive symptoms, a history of atopia, or the use of other drugs (legal or illegal). Physical examination was normal except for the presence of a nodule in the right breast at the site of the tuberculous abscess. She was informed that her symptoms might be caused by consumption of cheese and red wine intake in association with isoniazid use. She confirmed the regular consumption of different kinds of cheese, especially parmesan cheese; she denied consumption of black wine. The patient was advised to avoid eating cheese and TB treatment was maintained with rifampin and isoniazid; pyrazinamide and ethambutol were withdrawn at the end of the initial phase (2 months). Blood and urine examinations were requested. Serum electrolytes, bilirubin, transaminases, lactate dehydrogenase, thyroid hormones, haematological indices, prothrombin time, and urinary hydroxyindolacetic acid excretion over 24 hours were all within the normal range.

On her own initiative the patient decided to test the association of her symptoms with the ingestion of cheese. A few days later she ate a large amount of parmesan cheese: after 15 minutes she developed the typical reaction which lasted 1 hour. Thereafter she avoided eating ripened cheese and remained free of symptoms. She successfully completed her TB treatment course with no further adverse events.

The reaction to cheese described represents the ''tyramine syndrome'' or the so called ''cheese reaction''. Few such cases have been described previously in association with isoniazid treatment.[1–3] The syndrome is mainly characterised by skin flushing (facial, arms and upper body), tachycardia, dyspnoea, sweating, hypertension, conjuctival infection, and headache. The reaction is usually associated temporally with meals and is self-limiting, with signs and symptoms lasting from some minutes to a few hours.

Tyramine is formed by the decarboxylation of the amino acid tyrosine; oxidation by monoamine oxidase (MAO) represents the main pathway of its catabolism in man. In the gastrointestinal tract tyramine is oxidatively deaminated by MAO-A which seems to function as a protective barrier against high tyramine ingestion and high tyramine levels in the nervous system. Isoniazid is a weak inhibitor of MAO, mainly a MAO-A inhibitor. When the gastrointestinal and plasma MAO are inhibited by isoniazid and a large quantity of tyramine is ingested, it can be absorbed rapidly into the systemic circulation causing an abnormally high plasma concentration. Tyramine is then transported into adrenergic nerve terminals where it displaces norepinephrine (noradrenaline), causing its massive release and consequent hypertension.[4]

The concentration of tyramine in cheese is highly variable: higher concentrations are found in aged, ripened or spoiled cheeses like camembert, emmental and gruyere; moderate concentrations in Parmesan cheese; and it is undetectable in cream or cottage cheeses.[5] Most of the cases of ''cheese reaction'' described in the literature were induced by gruyere, parmesan and ''Swiss'' cheese. Unfortunately the cheese reaction cannot always be anticipated since it seems to be influenced by different kinds of factors such as the concentration of tyramine in the food or the bioavailability of isoniazid. Some authors have hypothesised that the rate of acetylation of isoniazid is a predisposing factor to the cheese reaction.[3] Slow acetylators should maintain higher plasma levels of isoniazid metabolites and consequently MAO inhibition for longer periods.

Clinicians treating patients with isoniazid should be aware of the risk of a reaction to foods rich in tyramine, especially cheese. This risk can be particularly relevant for patients from countries where cheese is part of the daily diets such as those in the Mediterranean area. Dietary restriction seems to be sufficient to control the recurrence of symptoms in patients who need to be maintained on isoniazid treatment for TB.

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References

1 **Hauser MJ**, Baier H. Interactions of isoniazid with foods. *Drug Intell Clin Pharm* 1982;**16**:617–8.
2 **Toutoungi M**, Carroll RL, Enrico JF, *et al*. Cheese, wine, and isoniazid. *Lancet*, 1985;ii, 671.
3 **Di Martini A**. Isoniazid, tricyclics and the ''cheese reaction''. *Int Clin Psychopharmacol* 1995;**10**:197–8.
4 **Hoffman BB**. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*.10th ed. New York: McGraw-Hill, 2001:220.
5 **McCabe BJ**. Dietary tyramine and other pressor amines in MAOI regimens: a review. *J Am Diet Assoc* 1986;**86**:1059–64.

NOTICE

Pharmacology of Asthma and COPD

A course on the Pharmacology of Asthma and COPD organised by Professor Peter Barnes will be held at Imperial College London at the National Heart & Lung Institute in collaboration with Royal Brompton Hospital on 22–25 November 2004. The course is suitable for physicians or scientists with an interest in the pharmacology and therapeutics of asthma and COPD. Enquiries to: Postgraduate Education Centre, National Heart & Lung Institute, Imperial College London, Guy Scadding Building, Royal Brompton Campus, Dovehouse Street, London SW3 6LY, UK. Telephone: 020 7351 8172. Fax: 020 7351 8246. Email: shortcourses.nhli@imperial.ac.uk.