

Masking of ^{13}C urea breath test by proton pump inhibitors is dependent on type of medication: comparison between omeprazole, pantoprazole, lansoprazole and esomeprazole

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Accepted for publication 3 May 2004

SUMMARY

Background: The need to withhold acid suppression therapy while awaiting urea breath test results is a common clinical problem in symptomatic patients. It is unclear at present if the dose or type of proton pump inhibitor or the type of test meal govern the apparent masking effect of proton pump inhibitors on the urea breath test.

Aim: To prospectively evaluate *Helicobacter pylori* detection rates during treatment with four different proton pump inhibitors, utilizing a high-dose citric acid-based ^{13}C urea breath test.

Methods: Patients positive for *Helicobacter pylori* by urea breath test were randomized to receive either omeprazole 20 mg/day, pantoprazole 40 mg/day, lansoprazole 30 mg/day or esomeprazole 40 mg/day for 14 days. A repeat breath test was performed on day 14 of treatment.

Results: One hundred and seventy-nine patients, mean age 45.8 ± 16.8 , completed the study. Treatment with omeprazole or pantoprazole prior to urea breath test (UBT) was associated with low false negative results, while lansoprazole and esomeprazole caused clinically unacceptable high false negative rates (pantoprazole 2.2% vs. lansoprazole 16.6%, $P = 0.02$, vs. esomeprazole 13.6%, $P = 0.05$; omeprazole 4.1% vs. lansoprazole 16.6%, $P = 0.05$).

Conclusions: Proton pump inhibitor-induced false negative results on high-dose citric acid based urea breath test vary with the type of proton pump inhibitor used. Selection of the appropriate test meal and proton pump inhibitor may allow symptomatic individuals to continue their proton pump inhibitors prior to performing a urea breath test.

INTRODUCTION

The introduction of proton pump inhibitors (PPIs) constitutes one of the most significant medical breakthroughs in the treatment of acid related disorders.

Inhibition of acid secretion from gastric parietal cells is achieved by blocking the H^+ , K^+ adenosine triphosphatase (ATPase) ion pump.¹ PPIs are highly effective in the treatment and symptomatic relief of peptic ulcer, gastro-oesophageal reflux disease, and as part of combination triple therapy for *Helicobacter pylori* eradication.^{2, 3} Few clinically significant differences have been found in the efficacy or adverse events rate between the three most prevalently prescribed and

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studied PPIs, lansoprazole (LAN), pantoprazole (PAN) and omeprazole (OME).^{1, 4} The recently introduced (S)-isomer of OME, esomeprazole (ESO), may provide more effective gastric acid control than standard doses of the other PPIs,⁵ but may not afford a better clinical response than other PPIs.^{6, 7}

The effect of PPIs on the results of the ¹³C UBT appears to be due to a pH-dependent mechanism.^{8–10} Previously published reports have described false negative rates of 17–38% for 20 mg/day OME after 14 days. Similar results were reported with the use of 30 mg/day LAN (Table 1).^{2, 3, 11} The effect of PAN is more controversial. Parente *et al.*¹² demonstrated that the use of 40 mg/day PAN for 14 days does not lead to false negative UBTs, whereas Dulbecco *et al.*, found significant false negative results using PAN.¹³ There is no data currently estimating the false negative UBT rate induced by ESO.

Difference in the effect of PPIs on UBT may also depend on factors other than the choice of PPI. We and others have recently published that the use of a test drink containing high dose citric acid may significantly decrease the false negative results associated with 14 days treatment by OME or PAN, independent of UBT methodology.^{14–16}

Based on previous studies, most centres currently recommend cessation of PPIs 7–14 days before UBT.^{17, 18} This requirement means that symptomatic patients have to defer therapy for a significant period of time in order to be tested. Ideally, for both clinical and quality of life concerns, patients and physicians would

prefer to start PPI treatment until the time of UBT. Based on previous observations, it may be possible to start or continue short term PPI therapy if the appropriate PPI and test meal do not significantly alter UBT results. The aim of this study was to prospectively evaluate the false negative rates of four different PPIs during UBT, using a high dose citric acid test meal.

MATERIALS AND METHODS

Study patients and protocol

A UBT (BreathID; Oridion, Jerusalem, Israel) was performed after a 3-h fast in patients over 18 years of age with upper gastrointestinal symptoms. Those with a positive UBT were included in the study. Exclusion criteria included: (i) administration of antibiotics and/or bismuth preparations within 4 weeks before the date of entry to the study, (ii) administration of PPIs within 4 weeks before the date of entry to the study, (iii) pregnant or breast-feeding women and (iv) previous gastric or oesophageal surgery. Patients were randomized to treatment with either OME 20 mg/day, PAN 40 mg/day, LAN 30 mg/day or ESO 40 mg/day, taken at 08:00 hours, 30–60 min before breakfast. A repeat breath test was performed on therapy at day 14, 1–3 h after patients received their last PPI dose. Patients were asked not to take antibiotics, bismuth compounds or to alter the recommended dose of the PPI. Compliance was checked by means of pill counts on day 14.

Patients with a negative UBT on day 14 underwent another UBT 2 weeks after PPI cessation, in order to clarify whether this was a false negative result, or alternatively, true eradication of the bacteria by PPI had occurred.

Urea breath tests

Informed consent was obtained from each patient before enrollment in the study. The study protocol was approved by the Institutional Review Board of the E. Wolfson Medical Center. This study was not supported by a commercial company. The effect of PPIs on the detection of *H. pylori* was examined by continuous real time UBT, (BreathID; Oridion).¹⁹ All patients ingested a test drink provided by the manufacturer that included 75 mg ¹³C-urea (tablet form of 99% ¹³C-enriched urea) with 4.0 g citric acid granulated based powder dissolved in 200 mL water. The cut-off point or threshold for the

Table 1. Summary of false negative urea breath test results induced by using standard doses of different proton pump inhibitors for 14 days. Comparison between omeprazole (OME), pantoprazole (PAN) and lansoprazole (LAN)

	Year of publication	Proton pump inhibitor	14 days false negative rates (%)
Chey <i>et al.</i> ³⁸	1996	OME 20 mg/day	5/13 (38)
Connor <i>et al.</i> ³⁹	1999	OME 20 mg/day	7/25 (28)
Savarino <i>et al.</i> ¹⁷	2000	OME 20 mg/day	5/30 (17)
Parente <i>et al.</i> ¹²	2002	OME 20 mg/day	12/40 (30)
Shirin <i>et al.</i> ^{14a}	2003	OME 20 mg/day	1/21 (5)
Parente <i>et al.</i> ¹²	2002	LAN 30 mg/day	8/41 (20)
Adachi <i>et al.</i> ⁴⁰	2003	LAN 30 mg/day	5/30 (17)
Parente <i>et al.</i> ¹²	2002	PAN 40 mg/day	0/42 (0)
Dulbecco <i>et al.</i> ¹³	2003	PAN 40 mg/day	3/28 (10.7)
Shirin <i>et al.</i> ^{14a}	2003	PAN 40 mg/day	0/22 (0)

^a Using high-dose citric acid as a test meal.

BreathID test has been determined to be 5 delta over baseline (DOB).

Data analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL, USA, 1999). Distributions of continuous variables were tested for normality using the Kolmogorov–Smirnov test. The DOB distributions after 2 weeks of PPI treatment significantly differed from normal, so non-parametric hypothesis testing was used. Spearman's rho correlation coefficients were calculated to describe associations between baseline and 2-week PPI (2w PPI) breath test values. Additionally, these associations were tested within each treatment assignment individually. UBT results were compared simultaneously across PPI treatment groups using the Kruskal–Wallis test and followed with *post hoc* pairwise testing using the Mann–Whitney *U*. The Fisher exact test was used to compare the rate of false negative results by PPI treatment and to determine whether false negative results differed by gender. The *t*-test for independent samples was used to examine age by false negative results at day 14. Logistic regression analysis was used to determine whether the baseline ^{13}C excretion predicted false negative results. All tests were considered significant at $P \leq 0.05$.

RESULTS

Patient data

Three hundred and eighty-six consecutive patients were tested by BreathID and 271 (69.9%) were found to be *H. pylori* positive. Of these, 59 were excluded

because of refusal to participate and 212 patients were enrolled in the study. None of the patients had significant chronic medical problems. During the study 33 patients were excluded because of PPI-induced side effects (mainly diarrhoea) or failure to return for follow-up testing after day 14 of PPI therapy. One hundred and seventy-nine patients (89 males and 90 females, mean age 45.8 ± 16.8 , range 18–85 years) completed the study with a full set of test data. Indications for *H. pylori* testing included, epigastric pain (51), gastro-oesophageal reflux disease (50), dyspepsia (28), peptic ulcer (14), vomiting (2), stool occult blood (1) and patient's request (33). All patients had complied fully with the medication schedule.

Urea breath tests

After 14 days of treatment 20 patients became negative. In a third breath test performed 2 weeks after cessation of PPIs, all but four of these patients with negative tests became positive, confirming that the initial result had been a false negative result. Of these 16 patients, seven received LAN (16.6%) and six received ESO (13.6%) while only two patients on OME (4.1%) and one on PAN (2.2%) demonstrated false negative results (overall $P = 0.04$). *Post hoc* pairwise comparisons revealed that subjects treated with PAN had significant fewer false negative results than LAN-treated subjects ($P = 0.02$) and significantly fewer false negatives than ESO-treated subjects ($P = 0.05$). Additionally, subjects treated with OME had fewer false negatives than LAN-treated subjects ($P = 0.05$). Significant differences in other pairwise comparisons were not detected (Table 2). There were no unifying parameters that characterized patients with a false negative response.

Table 2. False negative results at day 14 after proton pump inhibitor treatment. Comparison between omeprazole (OME), pantoprazole (PAN), lansoprazole (LAN) and esomeprazole (ESO)

Proton pump inhibitor	OME 20 mg	PAN 40 mg	LAN 30 mg	ESO 40 mg
Patients (<i>n</i>)	48	45	42	44
Male/female	20/28	24/21	24/18	21/23
Age (years \pm s.d.)	47.9 ± 16.7	45.9 ± 18.0	45.8 ± 16.8	49.0 ± 14.5
UBT results (DOB)				
Baseline	31.7 ± 31.6	27.5 ± 19.6	28.7 ± 23.7	23.8 ± 18.3
Day 14	33.8 ± 29.5	24.8 ± 21.4	27.1 ± 28.1	19.1 ± 17.5
False negative				
Day 14	2/48 (4.1%)*	1/45 (2.2%)**	7/42 (16.6%)	6/44 (13.6%)
True negative				
Day 14	0/48	1/45	0/42	3/44

* OME vs. LAN $P = 0.05$.

** PAN vs. LAN $P = 0.02$, PAN vs. ESO $P = 0.05$.

DOB, delta over baseline.

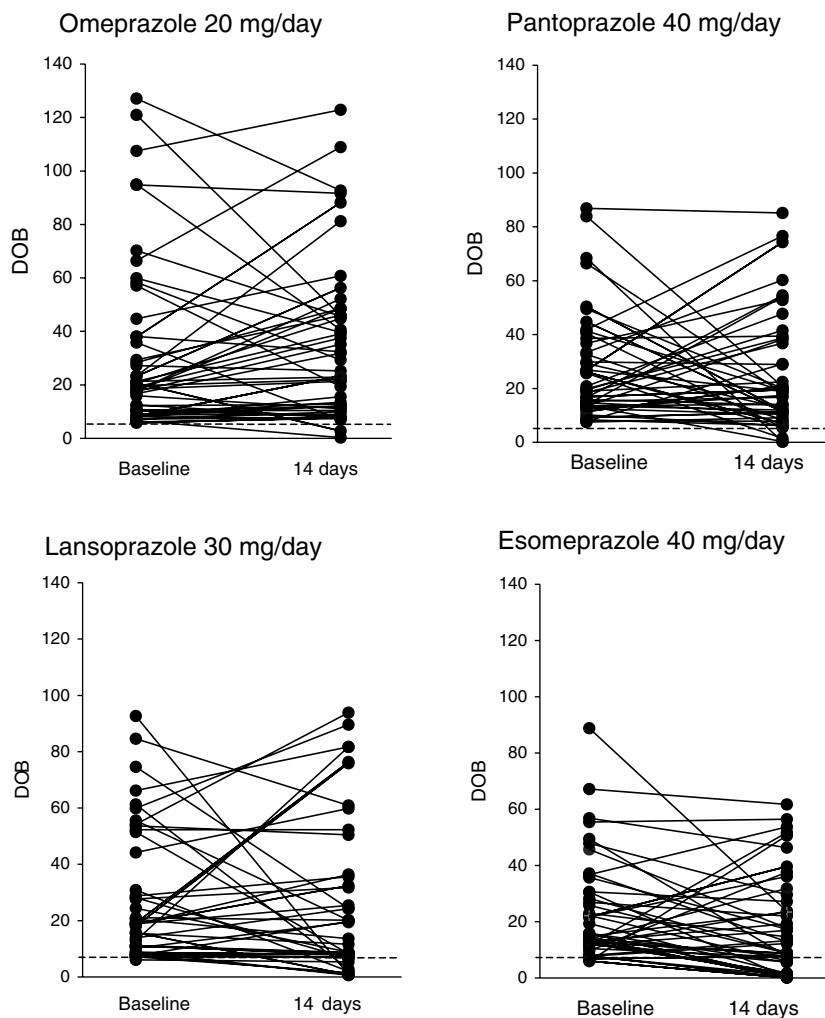


Figure 1. Individual values of delta over baseline (DOB) $^{13}\text{CO}_2$ excretion of 179 patients before acid suppressive therapy and the corresponding values after 14 days of treatment with omeprazole 20 mg/day, pantoprazole 40 mg/day, lansoprazole 30 mg/day and esomeprazole 40 mg/day.

Four patients (three on ESO and one on PAN) who became negative after 14 days, remained negative 2 weeks later, suggesting either the first UBT was falsely positive or alternatively that ESO and PAN had truly eradicated *H. pylori*. In a logistic regression model, baseline UBT results did not predict the false negative results at day 14. The DOB at 2 weeks did not differ significantly from baseline in the OME, PAN and LAN treatment groups, but it became significantly lower in the ESO group (23.8 ± 18.3 vs. 19.1 ± 17.5 , $P = 0.04$). Figure 1 demonstrates the individual subject UBT values in each group at baseline and 14 days after PPI therapy.

DISCUSSION

Symptomatic patients referred for ^{13}C UBTs, prior to *H. pylori* diagnosis, often have to refrain from taking

PPIs that could provide symptom relief, because of the risk of a false negative test. The results of the present study show that PPI-associated UBT masking can be kept to a minimum with judicious use of the appropriate PPI. Both PAN and OME had very low false positive rates (2–4%), whereas LAN and ESO had unacceptably high false negative rates ranging from 13 to 16%.

Variability between PPIs using the same dose of citric acid may be explained by two different mechanisms which influence detection of *H. pylori*. Inhibition of the bacterial urease activity secondary to alkalinization of the gastric content is one of the possible explanations for the false negative UBT induced by PPIs.^{20–23} Both urease activity and the transport of urea into the bacteria which is regulated by UreI-dependent specific H⁺-gated urea channels are pH dependent.²⁴ Urease activity is low at neutral pH, but as the external pH decreases to between 6.5 and 5.5 there is a 10–20-fold

increase in activity which remains high through approximately pH 2.5.^{20, 21} In this way, alkalization of gastric juice by PPIs may reduce both the entrance of urea into *H. pylori* and the activity of its cytoplasmic urease and consequently lead to false negative results.

Comparative studies demonstrated that PAN 40 mg/day and LAN 30 mg/day were more effective in inhibiting acid secretion in healthy volunteers than OME 20 mg/day, but were equally as effective as OME 40 mg/day.^{25, 26} probably reflecting dose differences. On the contrary, direct comparison between 30 mg LAN and 40 mg PAN revealed that despite the different doses, 30 mg/day LAN may produce a greater degree of acid inhibition than PAN 40 mg once daily.²⁷ Anderson *et al.* also demonstrated increased acid inhibitory effect of 20 mg ESO compared with 20 mg OME.²⁸

An alternative explanation is that PPIs directly inhibit the viability and growth of *H. pylori*.²⁹ Formation of sulphides of benzimidazoles as demonstrated in culture media³⁰ or direct inhibition of the bacterial urease activity may be the reasons for this selective antibacterial effect³¹ although growth inhibition has been reported also in urease negative *H. pylori* derivatives.³² Among the three PPIs, OME, LAN and PAN that have been compared for antibacterial activity, LAN was found to be the most potent and PAN the least active compound *in vitro*.^{33, 34} Gatta *et al.* compared the susceptibility of 52 *H. pylori* isolates to both OME and ESO. They found that 17 isolates were 2–64-fold more susceptible to ESO compared with only two isolates that were more susceptible to OME.³⁵

The rationale for the use of citric acid as an optimal test drink in UBT is not new. This is based on two characteristics: decrease of gastric pH and delay of gastric emptying.^{15, 16, 36, 37} These characteristics may optimize the test meal even during conditions which normally may cause a false negative breath test, such as use of OME.¹⁴ Previous studies using standard test meals with the same PPIs, presented in Table 1, have shown much higher and clinically unacceptable false negative rates varying from 17 to 38% for OME, 17 to 20% for LAN and up to 10.7% on PAN. These differences may be related to the effect of high dose citric acid on test results, although we did not evaluate this in our study.

We conclude that if a PPI needs to be administered when a UBT is performed, it is preferable to choose PAN or OME, even when using use a high dose of citric acid for the test. We surmise that the failure of high dose

citric acid to prevent LAN and ESO induced false negative UBTs may be explained by a combination of marked gastric acid suppression and antimicrobial activity of these compounds against *H. pylori*. Selection of the appropriate test meal and PPI may obviate the need to withhold therapy prior to performing UBTs.

REFERENCES

- Horn J. The proton pump inhibitors: similarities and differences. *Clin Ther* 2000; 22: 266–80.
- Savarino V, Neri M, Vigneri S. PPI-triple therapy in the eradication of *H. pylori* infection. *Gastroenterology* 1999; 117: 746–7.
- Stedman CAM, Barclay ML. Review article: comparison of pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment Pharmacol Ther* 2000; 14: 963–78.
- Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors. *Pharmacology and rationale for use in gastrointestinal disorders*. *Drugs* 1998; 56: 307–35.
- Scott LJ, Dunn CJ, Mallarkey G, Sharpe M. Esomeprazole: a review of its use in the management of acid related disorders. *Drugs* 2002; 62: 1503–38.
- Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. *Aliment Pharmacol Ther* 2003; 18: 587–94.
- Chey W, Huang B, Jackson RL. Lansoprazole and esomeprazole in symptomatic GERD. *Clin Drug Invest* 2003; 23: 69–84.
- Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB. Effect of proton-pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. *Ann Intern Med* 1998; 129: 547–50.
- Chey WD, Woods M, Scheiman JM, Nostrant TT, DelValle J. Lansoprazole and ranitidine affect the accuracy of the ¹⁴C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997; 92: 446–50.
- Greig MA, Neithercut WD, Hossack M *et al.* Suicidal destruction of *H. pylori* mediated by its urease activity. *Gut* 1990; 31: A600.
- Eaton KA, Brooks CL, Morgan DR *et al.* Essential role of urease in pathogenesis of gastritis induced by *Helicobacter pylori* in Gnotobiotic piglets. *Infect Immun* 1991; 59: 2470–5.
- Parente F, Sainaghi M, Sangaletti O, *et al.* Different effects of short-term omeprazole, lansoprazole or pantoprazole on the accuracy of the ¹³C-urea breath test. *Aliment Pharmacol Ther* 2002; 16: 553–7.
- Dulbecco P, Gambaro C, Bilardi C, *et al.* Impact of long-term ranitidine and pantoprazole on accuracy of [¹³C] urea breath test. *Dig Dis Sci* 2003; 48: 315–21.
- Shirin H, Frenkel D, Shevah O, *et al.* Effect of proton pump inhibitors on the continuous real time ¹³C-urea breath test. *Am J Gastroenterol* 2003; 98: 46–50.
- Chey WD, Chathadi KV, Montague J, Ahmed F, Murthy U. Intragastric acidification reduces the occurrence of false-negative urea breath test results in patients taking a proton pump inhibitor. *Am J Gastroenterol* 2001; 96: 1028–32.

- 16 Graham DY, Runke D, Anderson SY, Malaty HM, Klein PD. Citric acid as the test meal for the ¹³C-urea breath test. *Am J Gastroenterol* 1999; 94: 1214–17.
- 17 Savarino V, Bisso G, Pivari M *et al.* Effect of gastric acid suppression on ¹³C-urea breath test: comparison of ranitidine with omeprazole. *Aliment Pharmacol Ther* 2000; 14: 291–7.
- 18 Savarino V, Tracci D, Dulbecco P *et al.* Negative effect of ranitidine on the results of urea breath test for the diagnosis of *Helicobacter pylori*. *Am J Gastroenterol* 2001; 96: 348–52.
- 19 Shirin H, Kenet G, Shevah O *et al.* Evaluation of a novel continuous real time ¹³C urea breath analyzer for *Helicobacter pylori*. *Alimentary Pharmacol Ther* 2001; 15: 389–94.
- 20 Rektorschek M, Weeks D, Sachs G, Melchers K. Influence of pH on metabolism and urease activity of *Helicobacter pylori*. *Gastroenterology* 1998; 115: 628–41.
- 21 Scott DR, Weeks D, Hong C, Postins S, Melchers K, Sachs G. The role of internal urease in acid resistance of *Helicobacter pylori*. *Gastroenterology* 1998; 114: 58–70.
- 22 Pantoflickova D, Scott DR, Sachs G, Dorta G, Blum AL. ¹³C urea breath test (UBT) in the diagnosis of *Helicobacter pylori*: why does it work better with acid test meals? *Gut* 2003; 52: 933–7.
- 23 Meyer-Rosenberg K, Scott DR, Rex D, Melchers K, Sachs G. The effect of environmental pH on the proton motive force of *Helicobacter pylori*. *Gastroenterology* 1996; 111: 886–900.
- 24 Weeks DL, Eskandari S, Scott DR, Sachs G. A H⁺-Gated urea channel: the link between *Helicobacter pylori* urease and gastric colonization. *Science* 2000; 287: 482–5.
- 25 Bruley des Varannes S, Levy P, Lartigue S, Dellatolas F, Lemaire M, Galmiche JP. Comparison of lansoprazole with omeprazole on 24-hour intragastric pH, acid secretion and serum gastrin in healthy volunteers. *Aliment Pharmacol Ther* 1994; 8: 309–14.
- 26 Florent C, Forestier S. 24 monitoring of intragastric acidity between lansoprazole 30 mg and pantoprazole 40 mg. *Eur J Gastroenterol Hepatol* 1997; 9: 195–200.
- 27 Huang JQ, Goldwater DR, Thompson ABR, *et al.* Acid suppression in healthy subjects following lansoprazole or pantoprazole. *Aliment Pharmacol Ther* 2002; 16: 425–33.
- 28 Andersson T, Rohss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. *Aliment Pharmacol Ther* 2001; 15: 1563–9.
- 29 Graham DY, Opekun AR, Hammoud F, *et al.* Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol* 2003; 98: 1005–9.
- 30 Sjostrom JE, Kuhler T, Larsson H. Basis for the selective antibacterial activity in vitro of proton pump inhibitors against *Helicobacter* spp. *Antimicrob Agents Chemother* 1997; 41: 1797–801.
- 31 Nagata K, Satoh H, Iwahi T, Shimoyama T, Tamura T. Potent inhibitory action of the gastric proton pump inhibitor lansoprazole against urease activity of *Helicobacter pylori*: unique action selective for *H. pylori* cells. *Antimicrob Agents Chemother* 1993; 37: 769–74.
- 32 Nagata K, Takagi E, Tsuda M, *et al.* Inhibitory action of lansoprazole and its analogs against *Helicobacter pylori*: inhibition of growth is not related to inhibition of urease. *Antimicrob Agents Chemother* 1995; 3: 567–70.
- 33 Iwahi T, Satoh H, Nakao M, *et al.* Lansoprazole, a novel benzimidazole proton pump inhibitor, and its related compounds have selective activity against *Helicobacter pylori*. *Antimicrob Agents Chemother* 1991; 35: 490–6.
- 34 Nakao M, Malfertheiner P. Growth inhibitory and bactericidal activities of lansoprazole compared with those of omeprazole and lansoprazole against *Helicobacter pylori*. *Helicobacter* 1998; 3: 21–7.
- 35 Gatta L, Perna F, Figura N, *et al.* Antimicrobial activity of esomeprazole versus omeprazole against *Helicobacter pylori*. *J Antimicrobial Chemother* 2003; 51: 439–42.
- 36 Dominguez-Munoz JE, Leodolter A, Sauerbruch T, Malfertheiner P. A citric acid solution in an optimal test drink in the ¹³C-urea breath test for the diagnosis of *Helicobacter pylori* infection. *Gut* 1997; 40: 459–62.
- 37 Shiotani A, Saeed A, Yamaoka Y, Osato MS, Klein PD, Graham DY. Citric acid-enhanced *Helicobacter pylori* urease activity in vivo is unrelated to gastric emptying. *Aliment Pharmacol Ther* 2001; 15: 1763–7.
- 38 Chey WD, Spybrook M, Carpenter S, Nostrant TT, Elta GH, Scheinman JM. Prolonged effect of omeprazole on the ¹⁴C-urea breath tests. *Am J Gastroenterol* 1996; 91: 89–92.
- 39 Connor SJ, Seow F, Ngu MC, Katekaris PH. The effect of dosing with omeprazole on the accuracy of the ¹³C-urea breath test in *Helicobacter pylori*-infected subjects. *Aliment Pharmacol Ther* 1999; 13: 1287–93.
- 40 Adachi K, Fujishiro H, Mihara T, Komazawa Y, Kinoshita Y. Influence of lansoprazole, famotidine, roxatidine and rebamipide administration on the urea breath test for the diagnosis of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2003; 18: 168–71.