Journal of Gastroenterology and Hepatology (2003) **18,** 168–171

GASTRIC ACID SUPPRESSION AND *HELICOBACTER PYLORI* INFECTION

Influence of lansoprazole, famotidine, roxatidine and rebamipide administration on the urea breath test for the diagnosis of *Helicobacter pylori* infection

KYOICHI ADACHI, HIROFUMI FUJISHIRO, TAKAFUMI MIHARA, YOSHINORI KOMAZAWA AND YOSHIKAZU KINOSHITA

Department of Internal Medicine II, Shimane Medical University, Izumo, Japan

Abstract

Background and Aim: The sensitivity of the urea breath test (UBT) has been reported to be influenced by the administration of omeprazole, lansoprazole and ranitidine. However, it is unclear whether other H2 receptor antagonists (H2RA), except ranitidine, and rebamipide, a mucosal protective agent, affect UBT sensitivity. The aim of this study is to clarify the effects of lansoprazole, famotidine, roxatidine and rebamipide administration on UBT sensitivity.

Methods: Subjects comprised 30 volunteers with *Helicobacter pylori* infection. All subjects were examined by the ^{13}C-UBT on four occasions: (i) without medication (control); (ii) after the administration of 30 mg lansoprazole (u.i.d) for 14 days; (iii) after the administration of 100 mg rebamipide (t.i.d) for 14 days; and (iv) after the administration of 20 mg famotidine or 75 mg roxatidine (b.i.d) for 14 days. In the H2RA study, individuals were randomized into two groups of 15 subjects and were administered either famotidine or roxatidine.

Results: Five of the 30 cases administered lansoprazole and one of the 15 cases given roxatidine gave a false-negative UBT result. No negative UBT results were observed in patients administered famotidine or rebamipide.

Conclusion: Patients showing negative UBT results during the administration of proton pump inhibitors and H2RA should be re-examined after the cessation of these drugs to confirm the true negativity of *H. pylori* infection.

Key words: famotidine, *Helicobacter pylori*, lansoprazole, rebamipide, roxatidine, urea breath test.

INTRODUCTION

The urea breath test (UBT) is a simple, non-invasive, reproducible and accurate method for the diagnosis of *Helicobacter pylori* infection.[1–4] This test is commonly used for the assessment of *H. pylori* infection, particularly after eradication therapy.[5,6] As the UBT identifies the existence of *H. pylori* by detecting urease activity in the stomach, the results of the UBT are influenced by the administration of several drugs with antisecretory and/or anti-urease activity.[6–8] Several groups have investigated the effects of administration of proton pump inhibitors (PPI), omeprazole and lansoprazole, on the results of the UBT.[7,9–16] As omeprazole and lansoprazole have antimicrobial activity against *H. pylori*, as well as strong inhibitory activity on gastric acid secretion, administration of these drugs has been reported to decrease the sensitivity of the UBT.[7,9–16] Administration of ranitidine, a H2 receptor antagonist (H2RA), has also been reported to decrease UBT sensitivity in a dose-dependent manner.[13,17–20] However, it has not been fully investigated whether other H2RA, such as famotidine and roxatidine, affect the sensitivity of the UBT. In addition, it is unclear whether rebamipide, which has protective action against gastric mucosal injury and is commonly used in patients with gastric ulcers and gastritis in Japan,[21,22] influences UBT sensitivity. The influence of these anti-ulcer drugs on the sen-

Correspondence: Dr K Adachi, Department of Internal Medicine II, Shimane Medical University, 89-1 Enya-cho, Izumo-shi, Shimane 693-8501, Japan. Email: kadachi@shimane-med.ac.jp

Accepted for publication 21 August 2002.

sitivity of the UBT is clinically important, as these drugs are frequently used in patients with gastric ulcers where infection with *H. pylori* needs to be investigated. This study therefore investigated whether the administration of lansoprazole, famotidine, roxatidine and rebamipide for 14 days decreased the sensitivity of the UBT in subjects with *H. pylori* infection.

METHODS

Subjects

Thirty Japanese volunteers (29 men, one woman; mean age, 37.8 years) with *H. pylori* infection were recruited into this study, which was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects before entry into the study. All subjects gave positive UBT results, a positive serum immunoglobulin G antibody test with Immunis antipylori (Institute of Immunology, Tokyo, Japan), a positive *H. pylori* antigen test in stool samples with the HpSA EIA kit (Meridian Diagnostics, Cincinnati, OH, USA), and positive urine antibody tests with Urinelisa and Rapirun (Otsuka Pharmaceutical, Tokyo, Japan). No patient had dyspeptic symptoms or a history of gastrointestinal or hepatobiliary disease. No patient was taking medication on a regular basis at the time of this study. It was confirmed that none of the subjects had undergone previous eradication therapy for *H. pylori*. No subject had been using any drugs, such as PPI or antimicrobial medication, which might affect the status of *H. pylori* infection, for at least 1 month before starting the study protocol.

All subjects were examined by the ^{13}C-UBT on four occasions: (i) without medication (control); (ii) on the first day post-treatment with 30 mg lansoprazole (Takeprone; Takeda Chemical Industries, Osaka, Japan) u.i.d. (after breakfast) for 14 days; (iii) on the first day post-treatment with 100 mg rebamipide (Mucosta; Otsuka Pharmaceutical) t.i.d. (after meals) for 14 days; and (iv) on the first day post-treatment with famotidine 20 mg (Gaster; Yamanouchi Pharmaceutical, Tokyo, Japan) or roxatidine acetate hydrochloride 75 mg (Altat; Teikokuzouki Pharmaceutical, Tokyo, Japan) b.i.d. (after breakfast and supper) for 14 days. For administration of H2RA, individuals were randomly divided into two groups of 15 subjects and were administered either famotidine or roxatidine. The four UBT with and without medication were performed in a random order, allowing more than 4 weeks between each drug administration to eliminate any effects of the previous treatment.

All UBT were performed as described previously,[4,5] with minor modifications, after overnight fasting. [^{13}C]Urea (100 mg) dissolved in distilled water was administered. Subjects were instructed to maintain left lateral recumbence for 5 min, followed by a sitting position for 15 min. Breath samples before and 20 min after the administration of [^{13}C]urea were collected after a mouthwash. The [^{13}C]CO_2 concentration in breath samples was measured by using a ^{13}C analyzer (Ubit-IR200; Otsuka Electronics, Osaka, Japan). (Δ)^{13}C values (%) were analyzed. Subjects whose (Δ)^{13}C values were lower than 5% were regarded as negative in the UBT test.[5]

Statistical analyses of paired groups were performed by using the Wilcoxon signed rank test and Chi-squared test, and non-paired groups were compared by using the Mann–Whitney *U*-test. All analyses were performed with the aid of SPSS (6.1 J version for Macintosh; SPSS, Chicago, IL, USA). Differences at two-tailed $P < 0.05$ were considered to be statistically significant.

RESULTS

All 30 subjects in the present study completed the control UBT as well as UBT at the end of the three test regimens. All subjects were confirmed to show complete compliance by counting residual pills retained at the time of the UBT. Mean Δ values for the UBT and the number of cases in the two ranges of Δ values (<5 and ≥5%) in the four regimens are shown in Table 1. The variations of Δ values of UBT for each subject are shown in Figure 1. There was no significant difference in Δ values between the control and three drug regimens. However, the number of cases whose Δ value of UBT was <5% was significantly larger after the lansoprazole regimen than for the other two regimens. Five of 30 *H. pylori*-positive cases showed a negative UBT result after 14 days administration of 30 mg lansoprazole. Only one case in the H2RA regimen showed a negative UBT result. This false-negative case was in the

Table 1 Results of the urea breath test with and without 14 days administration of each anti-ulcer drug

	Without medication (control)	Lansoprazole	H2RA	Rebamipide
Mean ± SE of Δ value of UBT (%)	20.6 ± 2.5 (25.4 ± 4.1/15.9 ± 2.4)*	20.2 ± 2.8	25.5 ± 3.8 (35.6 ± 6.1/15.3 ± 2.9)*	20.2 ± 2.3
Δ value of UBT				
No. cases <5.0‰	0	5	1 (0/1)	0
No. cases ≥5.0‰	30 (15/15)	25	29 (15/14)	30

H2RA, H2 receptor antagonists. Data are the mean ± SE, and number of cases within each range of Δ value of urea breath test (UBT). Numbers in parentheses indicate the data for subjects who were treated with famotidine or roxatidine as H2RA (famotidine/roxatidine group). *Significant difference between the famotidine and roxatidine group.

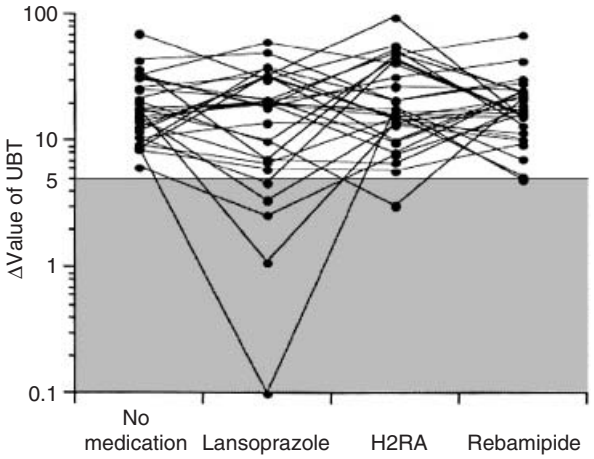

Figure 1 ΔValue of urea breath test for each subject without medication and on the first day post-treatment with the anti-ulcer drug. H2RA, H2 receptor antagonists; UBT, urea breath test.

roxatidine group, and the Δ value for the control baseline UBT was significantly lower in the roxatidine group than in the famotidine group. All six cases whose UBT showed a false-negative result after the administration of lansoprazole or roxatidine, showed over 5% of Δ value in the following UBT after the different regimens without and with different drugs. No case gave a negative UBT result, even after rebamipide administration.

DISCUSSION

Infection with *H. pylori* is known to be associated with several gastroduodenal diseases, including gastritis, peptic ulcer disease, gastric cancer and low-grade B-cell lymphoma of gastric mucosa-associated lymphoid tissue.[23–26] Therefore, many diagnostic methods for *H. pylori* infection have been developed, and numerous investigators have demonstrated the usefulness and accuracy of these tests. Of these tests, the UBT has been demonstrated to be the most useful and accurate method for the diagnosis of *H. pylori* infection, particularly in patients after they have received eradication therapy.[4–6] However, several factors have been demonstrated to affect the outcome of the UBT.[6] As patients with upper gastrointestinal symptoms are commonly treated with anti-ulcer drugs, the influence of anti-ulcer drugs on UBT results is a clinically important problem. Several investigators have demonstrated that the Δ values of UBT decreased and false-negative UBT results were observed during the administration of omeprazole, lansoprazole and ranitidine.[11–20] To help explain these observations, the intragastric acidity at the time of the UBT was considered to be of major importance.[27] Indeed, urease activity of *H. pylori* has been demonstrated to be reduced in an environment of neutral pH, and pretreatment with peroral citrate solution 30 min before the UBT was reported to reduce false-negative UBT results during the administration of ranitidine.[16]

The present study demonstrated that the false-negative UBT results occurred the morning after a 14-day course of lansoprazole. This result confirms those of several other reports, which demonstrated that omeprazole and lansoprazole negatively affected the results of the UBT.[11–16] This study also showed that false-negative UBT results occurred after the administration of roxatidine, a H2RA. In contrast, the administration of famotidine, another H2RA, did not affect the results of the UBT. Two possible mechanisms should be considered to explain the different effects of the two H2RA on the UBT results. One is the different potency in the antisecretory function of famotidine and roxatidine, which might affect UBT results, because the antisecretory effect of roxatidine at the dosage used in the present study was demonstrated to be superior to that of famotidine.[28] Another mechanism is the possible difference in *H. pylori* density between the subjects in the roxatidine- and famotidine-treated groups, because there were significant differences in control baseline Δ values of UBT between roxatidine- and famotidine-treated subjects. Therefore, further studies are required to confirm that administration of famotidine does not affect the UBT. Although the administration of ranitidine at higher doses was demonstrated to decrease UBT sensitivity,[19] our study clarified that the false-negative rate caused by H2RA administration was far lower than that caused by the administration of a PPI. Rebamipide, which has protective activity on the gastric mucosa, is widely used in patients with gastric ulcers and gastritis in Japan.[20,21] Administration of rebamipide for 14 days did not affect the results of the UBT, probably because rebamipide has no anti-urease or antisecretory activity.[20,21]

These results suggest that subjects with negative UBT results after administration of PPI and H2RA should be retested after cessation of these drugs. Chey *et al.* reported that the effects of lansoprazole and ranitidine administration on UBT values disappeared 5 days after cessation of these drugs.[13] In contrast, Laine *et al.* reported that administration of 30 mg lansoprazole induced false-negative UBT results in 33% of patients, and that this effect lasted for 7–14 days.[12] Savarino *et al.* also demonstrated that false-negative UBT results reverted to positive results 14 days after the cessation of ranitidine in all patients who gave false-negative UBT results during the administration of 300 mg ranitidine per day.[19] These finding indicate that cases with negative UBT results during administration of PPI and H2RA should be re-examined at least 14 days after the cessation of these drugs to confirm the true negativity of *H. pylori* infection.

In conclusion, the present study demonstrated that administration of lansoprazole and roxatidine negatively affected the sensitivity of the UBT, whereas administration of famotidine and rebamipide had no effect on the sensitivity of this test.

ACKNOWLEDGMENTS

We wish to thank Ms Rika Tohma, Ms Keiko Masuzaki (Department of Internal Medicine II, Shimane Medical

University), and Ms Yukiko Inoue (Katoh Hospital) for their technical support. This work was supported, in part, by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

REFERENCES

1 Graham DY, Klein PD, Evans DJ Jr *et al.* *Campylobacter pylori* detected noninvasively by the ^{13}C-urea breath test. *Lancet* 1987; **23**: 1174–7.

2 Marshall BJ, Plankey MW, Hoffman SR *et al.* A 20-minute breath test for *Helicobacter pylori*. *Am. J. Gastroenterol.* 1991; **86**: 438–45.

3 Logan RP, Polson RJ, Misiewicz JJ *et al.* Simplified single sample ^{13}carbon urea breath test for *Helicobacter pylori*: comparison with histology, culture, and ELISA serology. *Gut* 1991; **32**: 1461–4.

4 Miwa H, Murai T, Ohkura R *et al.* Effect of fasting subjects' posture on ^{13}C-urea breath test for detection of *Helicobacter pylori* infection. *Helicobacter* 1997; **2**: 82–5.

5 Miwa H, Ohkura R, Nagahara A *et al.* [^{13}C]-urea breath test for assessment of cure of *Helicobacter pylori* infection at 1 month after treatment. *J. Clin. Gastroenterol.* 1998; **27** (Suppl.): S150–3.

6 Vaira D, Holton J, Menegatti M *et al.* Review article: invasive and non-invasive tests for *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther.* 2000; **14** (Suppl. 3): 13–22.

7 Bravo LE, Realpe JL, Campo C, Mera R, Correa P. Effects of acid suppression and bismuth medications on the performance of diagnostic tests for *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 1999; **94**: 2380–3.

8 Klein PD, Malaty HM, Martin RF, Graham KS, Genta RM, Graham DY. Noninvasive detection of *Helicobacter pylori* infection in clinical practice: the ^{13}C urea breath test. *Am. J. Gastroenterol.* 1996; **91**: 690–4.

9 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.

10 Nakao M. Antibacterial properties of lansoprazole alone and in combination with antimicrobial agents against *Helicobacter pylori*. *J. Clin. Gastroenterol.* 1995; **20** (Suppl. 1): S32–7.

11 Chey WD, Spybrook M, Carpenter S, Nostrant TT, Elta GH, Scheiman JM. Prolonged effect of omeprazole on the 14C-urea breath test. *Am. J. Gastroenterol.* 1996; **91**: 89–92.

12 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.

13 Chey WD, Woods M, Scheiman JM, De Nostrant TTI, Valle J. Lansoprazole and ranitidine affect the accuracy of the ^{14}C-urea breath test by a pH-dependent mechanism. *Am. J. Gastroenterol.* 1997; **92**: 446–50.

14 Connor SJ, Seow F, Ngu MC, Katelaris PH. The effect of dosing with omeprazole on the accuracy of the ^{13}C-urea breath test in *Helicobacter pylori*-infected subjects. *Aliment. Pharmacol. Ther.* 1999; **13**: 1287–93.

15 El-Nujumi A, Hilditch TE, Williams C, McColl KE. Current or recent proton pump inhibitor therapy markedly impairs the accuracy of the [^{14}C]urea breath test. *Eur. J. Gastroenterol. Hepatol.* 1998; **10**: 759–64.

16 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.

17 Cutler AF, Elnaggar M, Brooks E, O'Mara K. Effect of standard and high dose ranitidine on [^{13}C]urea breath test results. *Am. J. Gastroenterol.* 1998; **93**: 1297–9.

18 Connor SJ, Ngu MC, Katelaris PH. The impact of short-term ranitidine use on the precision of the ^{13}C-urea breath test in subjects infected with *Helicobacter pylori*. *Eur. J. Gastroenterol. Hepatol.* 1999; **10**: 1135–8.

19 Savarino V, Bisso G, Pivari M *et al.* Effect of gastric acid suppression on ^{13}C-urea breath test: comparison of ranitidine with omeprazole. *Aliment. Pharmacol. Ther.* 2000; **14**: 291–7.

20 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.

21 Hayashi S, Sugiyama T, Amano K *et al.* Effect of rebamipide, a novel antiulcer agent, on *Helicobacter pylori* adhesion to gastric epithelial cells. *Antimicrob. Agents Chemother.* 1998; **42**: 1895–9.

22 Naito Y, Yoshikawa T, Iinuma S *et al.* Rebamipide protects against indomethacin-induced gastric mucosal injury in healthy volunteers in a double-blind, placebo-controlled study. *Dig. Dis. Sci.* 1998; **43** (Suppl. 9): S83–9.

23 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311–15.

24 Graham DY. Treatment of peptic ulcers caused by *Helicobacter pylori*. *N. Engl. J. Med.* 1993; **328**: 349–50.

25 Parsonnet J, Friedman GD, Vandersteen DP *et al.* *Helicobacter pylori* infection and the risk of gastric carcinoma. *N. Engl. J. Med.* 1991; **325**: 1127–31.

26 Isaacson PG, Spencer J. Is gastric lymphoma an infectious disease? *Hum. Pathol.* 1993; **24**: 569–70.

27 Scott DR, Weeks D, Hong C, Postius S, Melchers K, Sachs G. The role of internal urease in acid resistance of *Helicobacter pylori*. *Gastroenterology* 1998; **114**: 58–70.

28 Tanioka H, Kaga K. Comparison of roxatidine and famotidine on nocturnal gastric juice secretion. *J. Int. Med. Res.* 1996; **24**: 88–91.