• BRIEF REPORTS •

Capsule ^{13}C -urea breath test for the diagnosis of *Helicobacter pylori* infection

Nan-Jing Peng, Kwok-Hung Lai, Ren-Shyan Liu, Shui-Cheng Lee, Daw-Guey Tsay, Ching-Chu Lo, Huei-Hwa Tseng, Wen-Keui Huang, Gin-Ho Lo, Ping-I Hsu

Nan-Jing Peng, Daw-Guey Tsay, Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, China
Kwok-Hung Lai, Ching-Chu Lo, Gin-Ho Lo, Ping-I Hsu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, China
Huei-Hwa Tseng, Wen-Keui Huang, Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, China
Ren-Shyan Liu, Department of Nuclear Medicine, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, China
Shui-Cheng Lee, Institute of Nuclear Energy Research, Taoyuan, Taiwan, China

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Correspondence to: Dr. Ping-I Hsu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan, China. williamhsup@yahoo.com.tw
Telephone: +886-7-3422121-2075 Fax: +886-7-3461179
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Abstract

AIM: To compare the accuracy of capsule ^{13}C -urea breath test (UBT) with conventional invasive methods for the diagnosis of *Helicobacter pylori* infection.

METHODS: One hundred patients received CLO test, histological examination, culture and 100- or 50-mg capsule UBT for the diagnosis of *H. pylori* infection. *H. pylori* infection was defined as those with positive culture or positive results from both histology and CLO test.

RESULTS: Both the sensitivity and specificity of the 100-mg capsule UBT ($n = 50$) were 100%. The sensitivity and specificity of the 50-mg capsule UBT ($n = 50$) were 96.4 and 100%, respectively. Taken together, the accuracy of capsule UBT ($n = 100$) was higher than that of CLO test, histology and culture (100% vs 92%, 91% and 89%, respectively; $P = 0.035$, 0.018 and 0.005, respectively). Our data showed that the optimal timing of sampling for 100- and 50-mg capsule UBT was 15-30 and 6-15 min, respectively.

CONCLUSION: Capsule UBT has a higher accuracy compared with biopsy-based tests. It is an ideal method for the diagnosis of *H. pylori* infection.

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Key words: ^{13}C -urea breath test; Capsule; *Helicobacter pylori*; Oral urease

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INTRODUCTION

^{13}C -urea breath test (UBT) has become a highly reliable method for the non-invasive diagnosis of *Helicobacter pylori* (*H. pylori*) infection^[1-3]. It is the ideal test for those in whom endoscopy is not required because it offers the combination of simplicity, accuracy and absence of exposure to radioactivity^[3-6]. It is also a good method in monitoring treatment success following anti-*H. pylori* therapy, because it can avoid the false negative result from the biopsy-based tests due to patchy distribution of bacteria in the gastric mucosa and the false positive result from serology caused by previous *H. pylori* infection.

The principle of UBT is based on the high urease activity of *H. pylori* *in vivo*. The orally administered ^{13}C -labeled urea is readily hydrolyzed by urease of the organism to ammonia and $^{13}\text{CO}_2$. The latter can be detected through the collection of the expired samples. However, it is important to note that some urease-containing oral floras are also capable of hydrolyzing urea^[7,8]. The conventional UBT uses a liquid form of urea solution. On such way of urea ingestion, breath $^{13}\text{CO}_2$ may increase at an earlier sampling time after consumption due to the presence of oral urease^[8]. Cleansing mouths and delayed sampling collection at least 10 min after consumption are commonly used to avoid false positive results.

To prevent the effect of oral urease activity, we have previously developed an endoscopic UBT for the diagnosis of *H. pylori* infection. This diagnostic method applied ^{13}C -urea to the stomach through the working channel of endoscope, and thus could avoid contamination of urea from oral urease. Our data demonstrate that the new modality can rapidly discriminate between *H. pylori*-positive and *H. pylori*-negative patients at 2 min after the consumption of ^{13}C -urea with 100% of both sensitivity and specificity. Additionally, its diagnostic accuracy is significantly higher than that of culture, histology and CLO test^[9]. Nonetheless, endoscopic UBT is an invasive method for the diagnosis of *H. pylori* infection and it is not a good choice for the patients not requiring endoscopic examinations.

We therefore developed a capsule UBT to improve its clinical application. The patients swallowed urea-containing

capsules during the test to prevent the release of urea before reaching the stomach. The aims of this study were to compare the accuracy of capsule UBT with conventional methods for the diagnosis of *H pylori* infection and to find an optimal dosage and timing for sampling collection.

MATERIALS AND METHODS

Patients

From August 2001 to July 2003, 100 patients who attended the routine upper gastrointestinal endoscopy were included in the present study. Fifty-seven were males and 43 were females, aged 20-83 years. Criteria for exclusion included use of proton pump inhibitors within 1 mo before endoscopy, antibiotic ingestion within 1 mo before endoscopy, serious medical illness, and previous history of anti-*H pylori* therapy. Written informed consent was obtained from each subject. This study was approved by the Human Medical Research Committee of our hospital and by the Department of Health, Taiwan.

Upper gastrointestinal endoscopy, CLO test, histology and culture

During endoscopy, four gastric biopsy specimens were taken from lesser curvature 2 cm from the pylorus. Two specimens were fixed immediately in 10% neutral-buffered formalin for histological examination, one for urease test (CLO test, Delta-West, Bently, Australia), and the other for culture. Samples were sent to different laboratories that were blind to the results of other tests. The CLO test was monitored for color change up to 24 h after the addition of the gastric tissue. The gel was not warmed above ambient temperature at any time during the incubation period. The specimens for microbiological examination were transferred with brain heart infusion in ice and inoculated onto the CDC anaerobic blood agar (Becton Dickinson Microbiology System, Cockeysville, Maryland). The agar was incubated at 35 °C for 2 d in a micro-aerophilic gas mixture containing 5% O₂, 100 mL/L CO₂, and 85% N₂. Culture-positive patients were those with bacterial colonies grown in culture within 7 d. The organisms were identified as *H pylori* by Gram staining, colony morphology and positive oxidase, catalase and urease reaction. Histology-positive patients were those with curved organisms seen in H&E-stained sections under microscope. Although there is no real gold standard for the diagnosis of *H pylori*, cultures should be 100% specific if the procedures are performed properly. Use of culture alone as the gold standard may yield false negative results due to the inherent difficulties of culture. Hence, in the present study we defined patients with *H pylori* infection as those with positive culture or positive results from histology and CLO test.

Capsule UBT

The capsule UBT was done within 7 d of the endoscopy before antibiotic treatment was given. The ¹³C-urea, 99-atom% ¹³C-labeled urea, was produced by the Institute of Nuclear Energy Research (INER), Taiwan. Of the 100 patients, 50 received 100-mg capsule ¹³C-urea and 50 received 50-mg capsule ¹³C-urea. No test meal was used in this study. Patients were asked to fast for at least 6 h. A

baseline sample was collected in duplicate by breathing out through a straw into a 13 mL vacutainer tube. Patients then underwent a mouth washing by gargling to avoid the influence of oral urease, and received 100- or 50-mg capsule ¹³C-urea. Thereafter, patients were lying down and changing sides every 5 min. Breath samples were collected from the subjects 2, 4, 6, 8, 10, 15, 20, 25 and 30 min after ¹³C-urea consumption. All samples were sent to INER where a continuous flow isotope ratio mass spectrometer (CF-IRMS) (Europa Scientific Ltd, Crewe, UK) was used for analysis. One of the authors performed the analysis without knowing the results of the status of *H pylori* in the patients.

Values were expressed as an excess $\delta^{13}\text{CO}_2\text{‰}$ excretion. The $\delta^{13}\text{CO}_2$ is the ratio of ¹³C to ¹²C in the sample compared to the Pee Dee Belemnite (PDB) standard. The equation is given as: $\delta^{13}\text{CO}_2 = (R_{\text{sample}} - R_{\text{std}}) / R_{\text{std}} \times 1000$. R_{sample} and R_{std} represent the ratios of ¹³C to ¹²C in sample and standard, respectively. Excess $\delta^{13}\text{CO}_2$ is the value of $\delta^{13}\text{CO}_2$ detected at various time point minus that at the baseline.

Statistical analysis

Sensitivity, specificity and accuracy of capsule UBT were calculated for various cutoff values at different time points according to the predefined gold standard. The optimal cutoff value was determined by comparing the positions of the full curve in a graph from the receiver operating characteristic (ROC) curves^[10]. The optimal timing was defined as the time point at which the sums of the false negatives plus false positives were minimized. Student's *t* test was used for statistical analysis at different time points of UBT values. χ^2 test was used to determine the significance of differences between capsule UBT and biopsy-based modalities. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Capsule UBT

Table 1 shows the means and standard deviation of excess $\delta^{13}\text{CO}_2$ and *t* test values of the 100- and 50-mg capsule UBT at different time points. In the 50 cases that received 100-mg capsule ¹³C-urea, 18 were *H pylori*-positive and 32 *H pylori*-negative subjects. Breath ¹³CO₂ values were significantly higher in the *H pylori*-positive subjects than those in the *H pylori*-negative subjects from 2 min. According to the ROC curves, the sensitivity and specificity were both 100% at 15 min with a cutoff value of 5 $\delta^{13}\text{CO}_2\text{‰}$, and at 20-30 min with a cutoff value of 4-5 $\delta^{13}\text{CO}_2\text{‰}$. The optimal sampling time for discriminating *H pylori*-positive and *H pylori*-negative patients was accordingly between 15 and 30 min with 100% sensitivity and 100% specificity. In the 50 cases who received 50-mg capsule ¹³C-urea, 28 were *H pylori*-positive and 22 *H pylori*-negative subjects. Breath ¹³CO₂ values were significantly higher in the *H pylori*-positive subjects than those in the *H pylori*-negative subjects from 2 min (Table 1). The sum of the false negatives plus false positives was the smallest at 6-10 min with a cutoff value of 1 $\delta^{13}\text{CO}_2\text{‰}$ and at 15 min with a cutoff value of 1-2 $\delta^{13}\text{CO}_2\text{‰}$. Therefore, the optimal timing was between 6 and 15 min with 96.4% sensitivity and 100% specificity.

Table 1 Comparison of data from 100- and 50-mg capsule UBT at different time points

Method	2 min	4 min	6 min	8 min	10 min	15 min	20 min	25 min	30min
100-mg <i>H pylori</i> (+) UBT	4.15 (5.33) ^b	9.8 (11.02) ^b	13.29 (11.73) ^b	16.82 (14.03) ^b	19.37 (15.55) ^b	22.13 (14.89) ^{a,b}	23.57 (17.63) ^{a,b}	20.63 (15.23) ^{ab}	20.07 (15.29) ^{ab}
<i>H pylori</i> (-)	0.39 (1.08)	0.32 (0.58)	0.45 (1.66)	0.29 (1.32)	0.48 (1.42)	0.31 (1.05)	0.42 (1.08)	0.35 (0.87)	0.53 (0.9)
50-mg <i>H pylori</i> (+) UBT	1.8 (1.81) ^b	6.63 (5.39) ^b	9.95 (7.01) ^b	11.68 (7.48) ^b	12.17 (7.59) ^b	12.79 (7.29) ^b	13.17 (8) ^b	12.56 (8.02) ^b	11.62 (6.75) ^b
<i>H pylori</i> (-)	0.04 (0.33)	0.04 (0.29)	0.04 (0.31)	-0.01 (0.33)	0.01 (0.31)	-0.08 (0.35)	0.1 (0.46)	0.02 (0.39)	0.02 (0.42)

Values are in excess $\delta^{13}\text{CO}_2$ excretion‰: mean $\pm$ SD. ^a $P < 0.05$ (100-mg UBT *H pylori* (+) vs 50-mg UBT *H pylori* (+)), ^b $P < 0.01$ (*H pylori* (+) vs *H pylori* (-)).

Comparison of capsule UBT and biopsy-based modalities

Sensitivity, specificity and accuracy of all the diagnostic modalities used in the present study are shown in Tables 2–4. Compared with biopsy-based modalities, the accuracy of 100-mg capsule UBT was higher than that of the CLO test, histology and culture (Table 2, 100% vs 96%, 90 and 98%), although the differences were not statistically significant ($P > 0.05$). The sensitivity and accuracy of 50-mg capsule UBT were significantly higher than those of culture (Table 3, 96.4% vs 64.2%, $P = 0.005$; 98% vs 80%, $P = 0.008$).

Table 2 Sensitivity, specificity and accuracy of tests for the diagnosis of *H pylori* infection in patients with 100-mg capsule UBT

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CLO test ($n = 50$)	94.4 (17/18)	96.6 (31/32)	96 (48/50)
Histology ($n = 50$)	88.9 (16/18)	90.6 (29/32)	90 (45/50)
Culture ($n = 50$)	94.4 (17/18)	100 (32/32)	98 (49/50)
100-mg UBT ($n = 50$)	100 (18/18)	100 (32/32)	100 (50/50)

Table 3 Sensitivity, specificity and accuracy of tests for the diagnosis of *H pylori* infection in patients with 50-mg capsule UBT

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CLO test ($n = 50$)	82.1 (23/28)	95.5 (21/22)	88 (44/50)
Histology ($n = 50$)	92.9 (26/28)	90.9 (20/22)	92 (46/50)
Culture ($n = 50$)	64.2 (18/28) ^b	100 (22/22)	80 (40/50) ^b
50-mg UBT ($n = 50$)	96.4 (27/28)	100 (22/22)	98 (49/50)

^b $P < 0.01$ vs UBT.

Taken together (Table 4), the sensitivity of capsule UBT ($n = 100$) was significantly higher than that of culture (97.8% vs 76.1%, $P = 0.004$). It also had a higher specificity compared with histology (100% vs 90.7%, $P = 0.057$). Additionally, the accuracy of this new non-invasive modality was significantly higher than that of CLO test, histology and culture (99% vs 92%, 91 and 89%, respectively; $P = 0.035$, 0.018 and 0.005, respectively).

Table 4 Sensitivity, specificity and accuracy of tests for the diagnosis of *H pylori* infection in patients with 50- or 100-mg capsule UBT

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CLO test ($n = 100$)	87 (40/46)	96.3 (52/54)	92 (92/100) ^a
Histology ($n = 100$)	91.3 (42/46)	90.7 (49/54) ¹	91 (91/100) ^a
Culture ($n = 100$)	76.1 (35/46) ^b	100 (54/54)	89 (89/100) ^b
UBT ($n = 100$)	97.8 (45/46)	100 (54/54)	99 (99/100)

^a $P < 0.05$, ^b $P < 0.01$, ¹ $P = 0.057$ vs UBT.

DISCUSSION

Since ^{13}C -UBT was first described by Graham *et al.*^[11], attention has been drawn to its methodology. The protocol has been modified by several investigators to make its use easier and to improve its accuracy. According to our previous studies, the false-positive rates of the conventional UBT still range from 4.3 to 10.9%^[6,8]. In the present study, we demonstrated that capsule UBT was an extremely accurate method for the diagnosis of *H pylori* infection. The diagnostic accuracy of this new modality was significantly higher than that of CLO test, histology and culture. The sensitivity and specificity of capsule UBT were 97.8 and 100%, respectively. There were no false-positive cases because capsule UBT effectively avoided the contamination of urea from oral urease. Therefore, capsule UBT is probably an ideal method to diagnose *H pylori* infection.

In the present study, although breath $^{13}\text{CO}_2$ values of the *H pylori*-positive subjects were significantly greater than those of the *H pylori*-negative subjects at 2 min and later (Table 1), the optimal timing of capsule UBT for a good sensitivity and specificity was still at 6 min and later. This might be because the mean time between intake and complete capsule disintegration in the stomach is 3 min (1.5–4 min)^[12]. Furthermore, the swallowed saliva with oral urease activity may contribute to exhaled $^{13}\text{CO}_2$ as late as 30 min after ^{13}C -urea consumption^[8,12]. Therefore, according to the present study, the optimal sampling time for discriminating *H pylori*-positive and *H pylori*-negative patients is between 15 and 30 min on 100-mg capsule UBT and between 6 and 15 min on 50-mg capsule UBT.

In our study with 50-mg capsule UBT, breath $^{13}\text{CO}_2$ values were significantly higher in the *H pylori*-positive subjects than those in the *H pylori*-negative subjects from 2 min. The optimal timing for 96.4% sensitivity and 100% specificity was between 6 and 15 min. The efficacy of 50-mg capsule UBT to discriminate *H pylori*-positive group from *H pylori*-negative group was less than that with 100-mg capsule UBT (Table 1). The breath $^{13}\text{CO}_2$ values were significantly lower in the *H pylori*-positive subjects of 50-mg capsule UBT than in those of 100-mg capsule UBT from 15 to 30 min ($P < 0.05$). Several studies have suggested that the levels of *H pylori* too low to be detected by histology are usually associated with a negative UBT^[13,14]. Furthermore, the urease concentrations in different *H pylori* strains vary by up to eight-fold^[15,16]. Therefore, the less sensitive result might be due to the lower dosage of ^{13}C -urea in a weakly urease-positive bacterial strain or the low bacterial loads in the stomach of some infected patients. Capsule UBT

with 50 mg ^{13}C -urea may reduce the cost of the agent and maintain the specificity, but halving the dosage-reduced sensitivity of test.

Theoretically, endoscopic UBT is the most accurate method for the diagnosis of *H. pylori* infection since it avoids the influence of the urease activity in the oral cavity and can prevent the sampling bias by biopsy for histological examinations. In the previous study, we found that endoscopic UBT examination is a rapid and accurate method for the diagnosis of *H. pylori* infection, superior to the conventional UBT^[9]. Suto *et al*^[17], have found positive correlations between the endoscopic UBT values and the *H. pylori* colonization and activity score in the antrum and corpus, and negative correlations between the endoscopic UBT values and the atrophy and intestinal metaplasia scores in the corpus. Therefore, the values of test results are also able to reflect the bacterial load in the stomach. However, endoscopy is invasive and expensive, causes the patient discomfort, and introduces the risk of endoscopy cross-infection. Application of encapsulated urea has the same preventive effect of endoscopic UBT against the release of urea before reaching the stomach and the contamination of oral urease.

Biopsy-based tests have the possibility of sampling error and may cause false negatives. UBT effectively integrates the enzyme activity of bacteria over the entire surface of the stomach, and avoids the possibility of false-negative results. In this study, we demonstrated that the capsule UBT was a rapid and extremely accurate method for the diagnosis of *H. pylori* infection. The diagnostic accuracy was significantly higher than that of CLO test, histology and culture.

In conclusion, our study shows that capsule UBT is a simple, noninvasive, rapid and extremely accurate method for the diagnosis of *H. pylori* infection. It has a higher accuracy compared with biopsy-based tests and is probably the choice of method for the diagnosis of *H. pylori* infection. It merits further studies to compare capsule UBT with conventional UBT and stool antigen test.

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