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Twenty-minute 50 mg ^{13}C-urea breath test without test meal for the diagnosis of Helicobacter pylori *infection in Chinese*

W. M. WONG*, B. C. Y. WONG*, T. M. LI, K. W. WONG, K. L. CHEUNG, F. M. Y. FUNG, H. H. X. XIA & S. K. LAM

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

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SUMMARY

Background: We have previously shown that the 75 mg ^{13}C-urea breath test without citrate test meal is highly accurate for the diagnosis of *Helicobacter pylori* infection in Chinese subjects. A lower dose 50 mg ^{13}C-urea breath test protocol with a sampling time at 20 min has not been validated previously.

Aim: To investigate the accuracy of a 20-min 50 mg ^{13}C-urea breath test protocol in Chinese subjects.

Methods: Consecutive dyspeptic patients referred for upper endoscopy were recruited. ^{13}C-urea breath test was performed using (a) 75 mg and 50 mg of ^{13}C-urea on two separate days without a test meal, and (b) 50 mg of ^{13}C-urea with 2.4 g citrate as test meal, and compared with the gold standard [rapid urease test (CLO test) and histology]. Baseline, 20-min and 30-min breath samples were collected in all cases.

Results: Two hundred and six patients were tested. The accuracy of the 50 mg ^{13}C-urea breath test (no citrate) at 20 min and 30 min was 98%, comparable to that of the 50 mg ^{13}C-urea breath test with citrate (99.1%) and the 75 mg ^{13}C-urea breath test without citrate (100%).

Conclusions: A 20-min 50 mg ^{13}C-urea breath test without citrate produced highly accurate results for the diagnosis of *Helicobacter pylori* infection and is more economical and convenient for the Chinese population.

INTRODUCTION

The ^{13}C-urea breath test (^{13}C-UBT) is a technically simple and non-invasive test for the diagnosis of *Helicobacter pylori* (*H. pylori*) infection. The accuracy of the ^{13}C-UBT in diagnosing *H. pylori* infection is high, with a sensitivity of 90–98% and a specificity of 92–100%.[1–5] The sensitivity and specificity of post-treatment ^{13}C-UBT are as high as pre-treatment ^{13}C-UBT making it a reliable test for the determination of post-treatment *H. pylori* status.[6] Since it was first described by Graham *et al*. the test has been modified extensively, including variations in the dose of ^{13}C-urea, sampling time, test meal and the cut-off values.[7] The test meal in the ^{13}C-UBT was used to increase the residence time of ^{13}C-urea in the stomach and improve the contact between urease produced by *H. pylori* and ^{13}C-urea. Recently, citric acid has been proposed as the best liquid test meal.[8, 9] The 75 mg ^{13}C-UBT protocol has been validated in the Chinese population with a sensitivity and specificity of 96.5% and 97.7%, respectively, with citrate, and 94.7% and 97.7%, respectively, without citrate, using a delta-value of 5‰ and measurement interval of 30 min.[10] Thus citrate can be omitted without sacrificing the accuracy of the ^{13}C-UBT. Others have shown that a 20-min sampling point was similar to the 30-min sampling point for the fasting ^{13}C-UBT protocol. Lowering the dose of ^{13}C-urea and shortening the test interval have obvious advantages of reducing the cost of the ^{13}C-UBT.[11, 12]

Thus the aims of the present study were: (a) to investigate whether the 50 mg ^{13}C-urea protocol

Correspondence to: Dr B. C. Y. Wong, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong.
E-mail: bcywong@hku.hk
**Contributed equally to this work.*

without test meal is as accurate as the 75 mg ^{13}C-urea protocol; (b) to determine whether a shorter measurement interval of 20 min can be used; (c) to investigate the usefulness of the citrate test meal in the 50 mg ^{13}C-urea protocol.

METHODS

Patient population

Patients referred to the endoscopy unit of the Department of Medicine, Queen Mary Hospital, for the investigation of dyspepsia or for follow-up after *H. pylori* eradication and/or ulcer healing were recruited. Dyspepsia was defined as persistent or recurrent upper abdominal pain or discomfort over the preceding 3-month period. Informed written consent was obtained from all patients participating in the trial. Exclusion criteria included patients with previous gastric surgery and patients taking antibiotics, H_2 receptor antagonists, bismuth compounds or proton pump inhibitors in the 4 weeks before endoscopy. Patients with a past history of *H. pylori* eradication were allowed to enter the study provided that the medication for eradication had been stopped for at least 4 weeks and the other inclusion and exclusion criteria were met.

Gastric biopsies

During upper endoscopy, three antral biopsies and two corpus biopsies were taken. One antral biopsy was used for rapid urease test (CLO test) and the rest were sent for histological examination of *H. pylori* status by haematoxylin and eosin stains and modified Giesma staining if necessary. The definition of *H. pylori* infection in this study required both CLO test and histology to be positive and was used as the 'gold standard'. Equivocal cases were excluded from our analysis. This approach has been validated previously in our centre, with a sensitivity and specificity of 100%, and less than 1% of cases cannot be diagnosed by this method.[13]

^{13}C-UBT procedure

The study was divided into two parts. In the first part, 75 mg and 50 mg ^{13}C-UBTs without test meal were performed in consecutive patients after an overnight fast on two consecutive days (group I). After the collection of a baseline exhaled breath sample in a vacutainer, 75 mg and 50 mg ^{13}C-urea powder dissolved in 50 mL of water were given orally on day 1 and day 2, respectively. Further breath samples were taken at 20 and 30 min. In the second part of the study, 50 mg ^{13}C-UBTs with citrate as the test meal were performed in consecutive patients after an overnight fast (group II). The test meal used was 200 mL 0.1 N (2.4 g) citric acid solution. Ten minutes after ingestion of the test meal, a baseline exhaled breath sample was collected and followed by 50 mg ^{13}C-urea solution. Further breath samples were taken as stated previously. All patients were kept in the sitting position over the whole study period. All group I patients were recruited from 4 May 2000 to 15 August 2000, and all group II patients were recruited from 28 September 2000 to 14 November 2000. All recruited patients had not participated in any ^{13}C-UBT trials before. Collected samples were analysed by the purpose-built isotope ratio mass spectrometer in the Simon KY Lee Digestive Disease Laboratory, Queen Mary Hospital, Hong Kong. Results were expressed as delta over baseline (DOB). The sensitivities, specificities and accuracies of the ^{13}C-UBT with variation of the DOB cut-off levels were calculated at 20 and 30 min. The DOBs with the highest accuracy were obtained using the receiver operating characteristics (ROC) curve and the highest score (bold figure) in the accuracy column in Tables 1 and 2.

Statistical analysis

The statistics used included Student's *t*-test, chi-squared test and Fisher's exact test when appropriate. A P value of 0.05 or less was considered to be statistically significant.

RESULTS

One hundred and eleven patients (group I) and 108 patients (group II) were recruited in the first and second parts of the study, respectively. Thirteen cases were excluded from the analysis. Four cases lacked histology data and four cases could not be classified according to our gold standard for the diagnosis of *H. pylori* infection, i.e. only one positive or negative test out of the two. Five cases had incomplete data collection during the breath test analysis. Thus, a total of 206 patients (101 patients in group I and 105 patients in group II) were available for analysis. The mean age of these 206 patients was 48.9 years (range, 19–86 years). There were 97 males

and 109 females. Ninety-nine per cent of the study patients were ethnic Chinese. Two were Filipinos. Thirty-nine patients in group I and 18 patients in group II had a history of taking eradication therapy previously.

Ninety-nine patients (48%) were diagnosed as being *H. pylori*-positive by the gold standard. Of these 99 *H. pylori*-positive patients, 15 (15%) had gastric ulcer, 16 (16%) had duodenal ulcer, two (2%) had gastric and duodenal ulcers and 17 (17%) had gastro-duodenal erosions. One hundred and seven (52%) were *H. pylori*-negative by our gold standard. Of these 107 patients, three (3%) had duodenal ulcer, three (3%) had gastric ulcer, six (6%) had gastro-duodenal erosions, one (1%) had gastric polyp and one (1%) had oesophagitis. *H. pylori* status correlated strongly with the presence of gastric ulcers ($P < 0.001$), duodenal ulcers ($P < 0.001$) and gastro-duodenal erosions ($P < 0.001$).

The sensitivity, specificity and accuracy of the 75 mg and 50 mg ^{13}C-UBTs without test meals with variation of the DOB cut-off levels at 20 and 30 min are shown in Table 1. The highest accuracy for the 50 mg ^{13}C-UBT was 98%, using a DOB of 7.0–8.0‰ for the 20-min measurement and a DOB of 6.5‰ for the 30-min measurement. For the 75 mg ^{13}C-UBT, the highest accuracy was obtained with the 30-min measurement using a DOB of 3.5–4.5‰. The best cut-off values were confirmed by ROC analysis (data not shown). The sensitivity, specificity and accuracy of the 50 mg ^{13}C-UBT with citrate as the test meal with variation of the DOB cut-off levels at 20 and 30 min are shown in Table 2. Citric acid as a test meal for ^{13}C-UBT was well tolerated by all patients. The highest accuracy for the 50 mg ^{13}C-UBT with citrate was 99%, using a DOB of 3‰ for the 20-min measurement and a DOB of 2.5‰ for the 30-min measurement (confirmed by ROC analysis). Thus, citric acid drink shifted the DOB towards a lower value.

The DOB with the highest accuracy remained the same when the sensitivity, specificity and accuracy of the three ^{13}C-UBT protocols were calculated separately according to their eradication status (data not shown). Using the DOB with the highest accuracy, there was no difference in accuracy between the three ^{13}C-UBT protocols in patients before and after eradication therapy for the 20-min sampling point (see Table 3, P = N.S.).

The mean DOBs were significantly higher at the 20-min sampling point when compared to the 30-min sampling point for all three protocols (Figure 1) for *H. pylori*-positive and *H. pylori*-negative patients. However, there was no significant difference in the mean DOB between 50 mg ^{13}C-UBT with citrate and 50 mg ^{13}C-UBT without citrate at the 20- and 30-min sampling points. Thus, citric acid drink did not affect the mean DOB at the 20- and 30-min sampling points for the 50 mg ^{13}C-UBT protocol.

DISCUSSION

The ^{13}C-UBT is one of the most important non-invasive methods for the detection of *H. pylori* infection. The

Table 1. The sensitivity, specificity and accuracy of the ^{13}C-urea breath test using 75 mg ^{13}C-urea vs. 50 mg ^{13}C-urea, both without a test meal

	Sensitivity				Specificity				Accuracy			
	50 mg		75 mg		50 mg		75 mg		50 mg		75 mg	
DOB	20 min	30 min	20 min	30 min	20 min	30 min	20 min	30 min	20 min	30 min	20 min	30 min
3.0	**100**	**100**	**100**	**100**	78.8	92.3	73.1	94.2	89.1	96.0	86.1	97.0
3.5	**100**	98.0	**100**	**100**	78.8	92.3	84.6	**100**	89.1	95.0	92.1	**100**
4.0	**100**	98.0	**100**	**100**	88.5	94.2	90.4	**100**	94.1	96.0	95.0	**100**
4.5	**100**	98.0	**100**	**100**	88.5	96.2	**92.3**	**100**	94.1	97.0	**96.0**	**100**
5.0	**100**	98.0	**100**	98.0	92.3	96.2	**92.3**	**100**	96.0	97.0	**96.0**	99.0
5.5	**100**	98.0	98.0	98.0	94.2	96.2	**92.3**	**100**	97.0	97.0	95.0	99.0
6.0	**100**	98.0	98.0	95.9	94.2	96.2	**92.3**	**100**	97.0	97.0	95.0	98.0
6.5	**100**	98.0	98.0	93.9	94.2	**98.1**	**92.3**	**100**	97.0	**98.0**	95.0	97.0
7.0	**100**	95.9	98.0	93.9	**96.2**	**98.1**	**92.3**	**100**	**98.0**	97.0	95.0	97.0
7.5	**100**	95.9	98.0	93.9	**96.2**	**98.1**	**92.3**	**100**	**98.0**	97.0	95.0	97.0
8.0	**100**	95.9	98.0	93.9	**96.2**	**98.1**	**92.3**	**100**	**98.0**	97.0	95.0	97.0

Figures in bold, highest score within each column. DOB, delta over baseline.

Table 2. The sensitivity, specificity and accuracy of the ^{13}C-urea breath test using 50 mg ^{13}C-urea with 2.4 g citrate as the test meal

	Sensitivity		Specificity		Accuracy	
DOB	20 min	30 min	20 min	30 min	20 min	30 min
2.0	**100**	**100**	81.8	94.5	90.5	97.1
2.5	**100**	**100**	90.9	98.2	95.2	**99.0**
3.0	**100**	96.0	**98.2**	98.2	**99.1**	97.1
3.5	96.0	96.0	**98.2**	98.2	97.1	97.1
4.0	94.0	94.0	**98.2**	98.2	96.2	96.2
4.5	94.0	94.0	**98.2**	98.2	96.2	96.2
5.0	94.0	90.0	**98.2**	98.2	96.2	94.3
5.5	92.0	90.0	**98.2**	98.2	95.2	94.3
6.0	92.0	90.0	**98.2**	98.2	95.2	94.3
6.5	90.0	88.0	**98.2**	98.2	94.3	93.3
7.0	90.0	86.0	**98.2**	98.2	94.3	92.4
7.5	90.0	86.0	**98.2**	**100**	94.3	93.3
8.0	88.0	86.0	**98.2**	**100**	93.3	93.3

Figures in bold, highest score within each column. DOB, delta over baseline.

Table 3. Accuracy of the three different ^{13}C-urea breath test protocols in patients before and after eradication therapy using the best delta over baseline (DOB) value at the 20-min sampling point

	75 mg ^{13}C no meal (before triple)	75 mg ^{13}C no meal (after triple)	50 mg ^{13}C no meal (before triple)	50 mg ^{13}C no meal (after triple)	50 mg ^{13}C citrate (before triple)	50 mg ^{13}C citrate (after triple)
DOB	4.5	4.5	7.5	7.5	3.0	3.0
Accuracy	61/62	36/39	61/62	38/39	86/87	18/18
	98.4%	92.3%	98.4%	97.4%	98.9%	100%
P value	0.943		0.973		0.975	
Odds ratio	1.01		1.01		0.989	
95% CI	0.60–1.89		0.57–1.79		0.48–2.03	

75 mg ^{13}C-UBT protocol has been validated in the Chinese population previously with an accuracy of 96–97%, and a test meal can be safely omitted without sacrificing accuracy.[8] Decreasing the dose of ^{13}C-urea and shortening the test interval allows a reduction of the cost of the test and makes it more convenient. This is particularly important for developing countries, such as China, in terms of cost saving. It potentially allows a wider application of this non-invasive test for the diagnosis of *H. pylori* infection in such a high-risk region. Thus, we investigated whether lowering the dose of ^{13}C-urea to 50 mg and shortening the sampling point to 20 min was a feasible approach for this purpose.

We found that the accuracy of the 50 mg ^{13}C-UBT without citrate at 20 min and 30 min was 98%, comparable with the accuracy of the 75 mg ^{13}C-UBT protocol without citrate. The use of 50 mg ^{13}C-urea reduces the cost by 33% compared to the use of 75 mg ^{13}C-urea. Thus, the 50 mg ^{13}C-urea protocol is a cost-saving method for the diagnosis of *H. pylori* infection in the Chinese population. Although the costs of packing and weighing out the ^{13}C-urea remain the same, the reduction in the cost of ^{13}C-urea is still attractive for high volume centres.

At present, there is universal agreement that two samples should be taken: a basal sample collected at time zero and a 30-min sample collected after the ingestion of ^{13}C-urea. ^{13}C is measured as the $^{13}CO_2$:$^{12}CO_2$ isotope ratio and is expressed as DOB. The best DOB in the three ^{13}C-UBT protocols was determined by the combination of ROC analysis and the highest score (bold figure) obtained in the accuracy column in Tables 1 and 2. Thus, the best DOB values for the 50 mg ^{13}C-UBT without citrate were 7.0–8.0‰ for the 20-min measurement and 6.5‰ for the 30-min measurement (Table 1), while the best DOB values for the 50 mg ^{13}C-UBT with citrate were 3.0‰ for the 20-min measurement and 2.5‰ for the 30-min measurement (Table 2). For the 75 mg ^{13}C-UBT without citrate, the best DOB was 3.5–4.5‰ (Table 1).

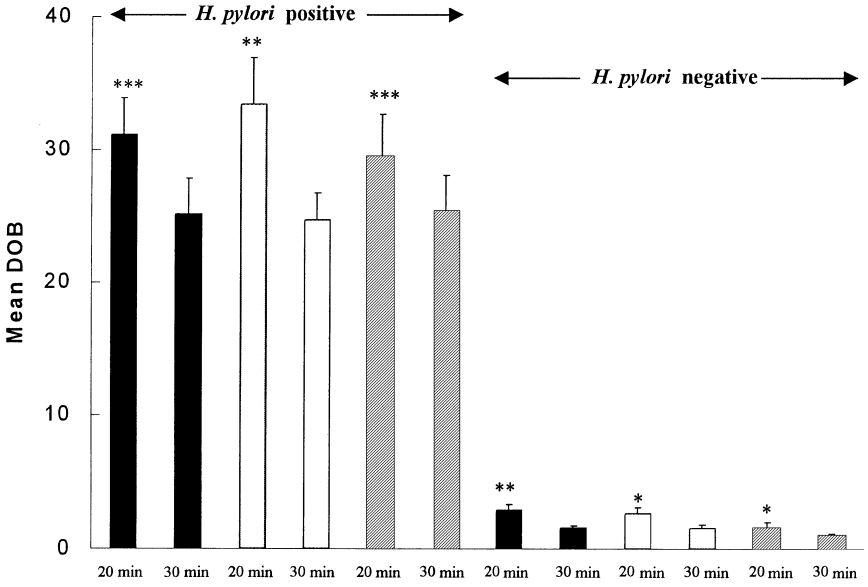

Figure 1. Mean delta over baseline (DOB) with or without test meals in *Helicobacter pylori* (*H. pylori*)-positive and *H. pylori*-negative subjects at 20- and 30-min sampling points. ■, 75 mg ^{13}C-UBT (no meal); □, 50 mg ^{13}C-UBT (no meal); ▨, 50 mg ^{13}C-UBT (citrate). ***$P < 0.001$ when compared with mean DOB at 30 min. **$P < 0.01$ when compared with mean DOB at 30 min. *$P < 0.05$ when compared with mean DOB at 30 min.

From the present study, we found that there was no difference in accuracy between the 20-min and 30-min sampling points for the 50 mg ^{13}C-UBT protocol without citrate. Thus shortening the measurement interval to 20 min after the basal sample is possible without sacrificing accuracy. This finding was similar to that described by Miwa *et al.* and Malaty *et al.* but the amounts of ^{13}C-urea used in their studies were 100 mg and 125 mg, respectively.[11, 12]

The mean DOB was similar for 50 mg ^{13}C-UBT with or without citrate at the 20-min and 30-min sampling points. This finding correlated well with our previous report using 75 mg ^{13}C-urea as the substrate and 2.4 g citrate as the test meal, in which the mean DOB was similar for ^{13}C-UBT with or without citrate at all time intervals from 15 to 60 min.[10] This appears to be a unique observation in the Chinese population and is possibly related to the difference in the distribution, delivery and emptying of ^{13}C-urea. A similar observation was reported with regard to the parietal cell mass and acid secretory capacity of Asian patients with duodenal ulcer, which are only slightly more than half the values of Caucasian patients despite correction for body stature.[14] Furthermore, ethnic differences in gastric emptying have been reported previously.[15] Further physiological studies on gastric emptying in the Chinese population are warranted.

The use of a test meal in ^{13}C-UBT was employed to increase the residence time of ^{13}C-urea in the stomach and improve the contact between urease produced by *H. pylori* and the substrate; citric acid has been suggested as the best liquid test meal.[8, 9, 16] Citric acid drink shifted the best DOB of the 50 mg ^{13}C-UBT from a higher value towards a lower value for both the 20-min (7.0–8.0‰ to 3.0‰) and 30-min (6.5‰ to 2.5‰) sampling points (Tables 1 and 2). The optimal cut-off value between *H. pylori*-infected subjects and *H. pylori*-uninfected subjects for the 50 mg ^{13}C-urea protocol has been under-described in the literature. Sheu *et al.* reported a sensitivity of 96.4% and specificity of 98.9% for a 50 mg ^{13}C-UBT protocol with citrate as test meal using a cut-off point of 3.5‰.[17] The best DOB found for our 50 mg ^{13}C-UBT with citrate correlated well with Sheu *et al.*'s study. The accuracy of the 50 mg ^{13}C-UBT protocol with citrate was similar to that of the 50 mg ^{13}C-UBT without citrate. Thus the citrate test meal can be safely omitted without sacrificing accuracy.[11, 12] We therefore conclude that, in the Chinese population, the best cut-off value for the 50 mg ^{13}C-urea protocol with citrate test meal at 20 min is 3.0‰, while the best cut-off value for that without test meal at 20 min is 7.0–8.0‰.

It may be argued that the number of patients is too small for a sufficient evaluation of this modified protocol in patients with previous eradication therapy. However, judging from the 95% confidence interval, as shown in Table 3, the range was actually rather narrow. Further studies are warranted to fully evaluate this protocol in post-eradication patients.

In conclusion, we have shown that 50 mg ^{13}C-UBT with or without test meal using a sampling point at

20 min is highly accurate for the diagnosis of *H. pylori* infection in the Chinese population. This protocol is more economical and less time consuming for the diagnosis of *H. pylori* infection in the Chinese population, and has potential wider application in other parts of Asia.

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