A new, practical, low-dose ^{14}C-urea breath test for the diagnosis of *Helicobacter pylori* infection: clinical validation and comparison with the standard method

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Abstract. The carbon-14 urea breath test (UBT) is a reliable and non-invasive technique for the diagnosis of *Helicobacter pylori* (HP) infection. In this study we evaluated the diagnostic performance of a new, practical and low-dose ^{14}C-UBT system for the diagnosis of HP and compared the results with those obtained using the standard method. Seventy-five patients (56 female, 19 male) with dyspepsia underwent ^{14}C-UBT and endoscopy with antral biopsies for histological analysis. The rapid urease test (CLO test) was applied to 50 of these patients. After a 6-h fasting period, a 37-kBq ^{14}C-urea capsule was swallowed for UBT. Breath samples were collected and counted using two different methods, the Heliprobe method and the standard method. In the Heliprobe method, patients exhaled into a special dry cartridge system (Heliprobe BreathCard) at 10 min. The activities of the cartridges were counted using a designated small GM counter system (Heliprobe analyser). Results were expressed both as counts per minute (HCPM) and as grade (0, not infected; 1, equivocal; 2, infected) according to the counts. In the standard method, breath samples were collected by trapping in a liquid CO_2 absorber. Radioactivity was counted as disintegrations per minute (SDPM) using a liquid scintillation counter after addition of a liquid scintillation cocktail. Histological examination was used as a gold standard. Two patients were excluded from the study because of inadequate biopsy sampling. Forty-eight patients (65%) were found to be HP positive on histology. The Heliprobe method correctly classified 48 of 48 HP-positive patients and 19 of 25 HP-negative patients (sensitivity 100%, specificity 76%, PPV 88%, NPV 100%, accuracy 91%). The standard method correctly classified 48 of 48 HP-positive patients and 20 of 25 HP-negative patients (sensitivity 100%, specificity 80%, PPV 90%, NPV 100%, accuracy 93%). On the other hand, the CLO test identified 26 of 32 HP-positive and 12 of 16 HP-negative patients (sensitivity 81%, specificity 75%, PPV 86%, NPV 66%, accuracy 79%). With the Heliprobe method, all of the positive results were grade 2, and all of the negative results were grade 0. No patients were defined as having grade 1 results. Counts allowed clear discrimination of HP-positive and -negative patients with both methods, the difference being statistically significant in each case (P<0.001). A significant correlation was found between HCPM and SDPM (r 0.863, P<0.001). According to the ROC analysis, the area under the curve was nearly the same with HCPM (AUC, 0.888; 95% CI, 0.785–0.992) and SDPM (AUC, 0.898; 95% CI, 0.802–0.994). In conclusion, the new ^{14}C-UBT system is a highly accurate method for the diagnosis of HP infection. It is rapid and practical, and therefore suitable for clinical and office practice.

Keywords: Helicobacter pylori – Carbon-14 urea breath test – Peptic ulcer disease

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Introduction

Helicobacter pylori (HP) is a spiral, gram-negative bacterium that has been found to be associated with gastritis, peptic ulcer disease, gastric adenocarcinoma and MALT lymphoma [1, 2, 3]. There is consequently increasing demand for treatment and a great need for simple and accurate methods for the diagnosis of HP infection.

Invasive diagnostic methods require mucosal biopsy during endoscopy, with the specimens being subjected to culture, rapid urease test, polymerase chain reaction or histological analysis. Non-invasive methods include antibody detection (serology), stool antigen test and urea breath test (UBT). While serology (ELISA) is simple and easy to perform, it is not a reliable test for the diagnosis of HP infection in elderly people or for determination of eradication of HP, since it remains positive for a long period despite adequate treatment [4, 5].

The production of high amounts of urease by HP has been used in the development of UBTs. An oral dose of urea is rapidly broken down by HP in the gastric mucosa to ammonia and carbon dioxide. Labelled carbon dioxide derived from labelled urea can be detected in the breath as a marker of infection. UBTs with either carbon-13 or carbon-14 urea are non-invasive methods, sample the whole stomach and reflect the actual status of infection. Both tests are highly accurate, with reported sensitivities of 97–100% and specificities of 95–100% for both diagnosis and proof of eradication of HP infection after therapy [1, 2, 6, 7, 8, 9]. While the two isotopes seem to offer similar diagnostic accuracy, ^{13}C-UBT has the inconvenience of requiring (a) more complex and expensive equipment on site or else analysis off-site by an external laboratory and (b) administration of a test meal and cold urea to the patient. These are not necessary with ^{14}C, and the test is thus simpler, faster and cheaper.

The routine test protocol of ^{14}C-UBT requires ingestion of ^{14}C-urea, collection of breath samples at frequent intervals using a liquid CO_2 trapping medium, addition of a liquid scintillation cocktail and counting with a β-scintillation counter. Several different methodological approaches have been suggested to simplify the UBT. Recently a new, practical dry breath collection cartridge (Heliprobe BreathCard) and counting system (Heliprobe analyser) have been developed for this purpose.

In this prospective study we evaluated the diagnostic performance and accuracy of this new ^{14}C-UBT system and compared the results with those of the rapid urease test (CLO test) and the standard (liquid CO_2 absorber and liquid scintillation counting) method.

Materials and methods

Patients. Seventy-five patients (56 female, 19 male; mean age 41±14 years) with dyspepsia were included in the study. Informed consent was obtained from each patient. All patients underwent upper gastrointestinal endoscopy as well as ^{14}C-UBT within 1 week. CLO test was applied to 50 of these patients.

Rapid urease test (CLO) test and histological examination. During upper gastrointestinal endoscopy, three biopsy specimens were taken from antral mucosa, one for CLO test and two for histological analysis. A home-made kit was used for the CLO test. One biopsy specimen was placed in a test tube and the colour reaction was read after 6 h. Histology samples were fixed in formalin, embedded in paraffin, sectioned in routine fashion and stained with Giemsa.

14C-urea breath test. Antacids were stopped at least 24 h before the test, sucralfate and H_2 receptor antagonists were discontinued for 1 week before the test, and proton pump inhibitors, bismuth compounds and antibiotics were stopped for 1 month beforehand. After overnight fasting, patients swallowed 37 kBq (1 μCi) of an encapsulated form of ^{14}C-urea/citric acid composition (Helicap, Noster System AB Stockholm, Sweden) with 25 ml water. Breath samples were collected and counted using two different methods:

1. *Heliprobe method:* Breath samples of patients were collected with a special dry cartridge system (Heliprobe BreathCard, Noster System AB Stockholm, Sweden) at 10 min. Patients exhaled gently into the cartridge mouthpiece until the indicator membrane changed colour from orange to yellow. The breathcard was inserted into a special small desktop Geiger-Müller counter (Heliprobe-analyser, Noster System AB Stockholm, Sweden) and activity counted for 250 s. Results were expressed both as counts per minute (HCPM) and as grade (0: not infected, CPM <25; 1: equivocal, CPM 25–50; 2: infected, CPM >50), as suggested by the producer according to the counts obtained from the cartridges.
2. *Standard method:* After completion of the breath sample collection in method 1, patients were asked to blow through a drinking straw into a 20-ml glass scintillation vial containing 0.1 ml CO_2 absorber solution (Carba Sorb E, packard) as well as a trace of the pH indicator thymolphthalein. Sampling was considered complete when the colour of the solution changed from blue to colourless. After addition of 10 ml of liquid scintillation cocktail (Pico-flour 40, Packard), radioactivity was counted for 10 min in a liquid scintillation counter (tri-carb 2500 TR, Packard). Counts were corrected to disintegrations per minute (SDPM) using an external standard method. The cut-off value was chosen as 100 DPM for the standard method in accordance with the results of our previous biopsy-controlled study.

Data analysis and statistics. Both ^{14}C-UBT methods and the CLO test were validated against histological examination, and their sensitivity, specificity, positive/negative predictive values (PPV, NPV) and accuracy were determined.

The HCPM and SDPM counts of HP-positive and -negative patients were compared using the Mann-Whitney *U* test. Spearman's correlation and ROC curve analysis were performed for comparison of HCPM and SDPM counts.

All statistical analyses, except for the diagnostic performance values, were performed with Systat (ver.10) statistical package (SPSS, Chicago, IL).

Table 1. Comparative results of histology, the CLO test, the Heliprobe method and the standard method

Histology	CLO test		Heliprobe UBT		Standard UBT	
	(+)	(–)	(+)	(–)	(+)	(–)
HP (+)	26	6	48	–	48	–
HP (–)	4	12	6	19	5	20

Table 2. Diagnostic performance of the tests

	CLO test	Heliprobe UBT	Standard UBT
Sensitivity (%)	81	100	100
Specificity (%)	75	76	80
Positive predictive value (%)	86	88	90
Negative predictive value (%)	66	100	100
Accuracy (%)	79	91	93

Table 3. The HCPM and SDPM values of *Helicobacter pylori*-positive and -negative patients

	HP (+)	HP (–)
HCPM	269 (300, 69–770)[a]	10 (72, 0–617)
SDPM	745 (1,104, 220–3,747)	34 (216, 4–1,422)

[a] Median (mean, minimum–maximum)

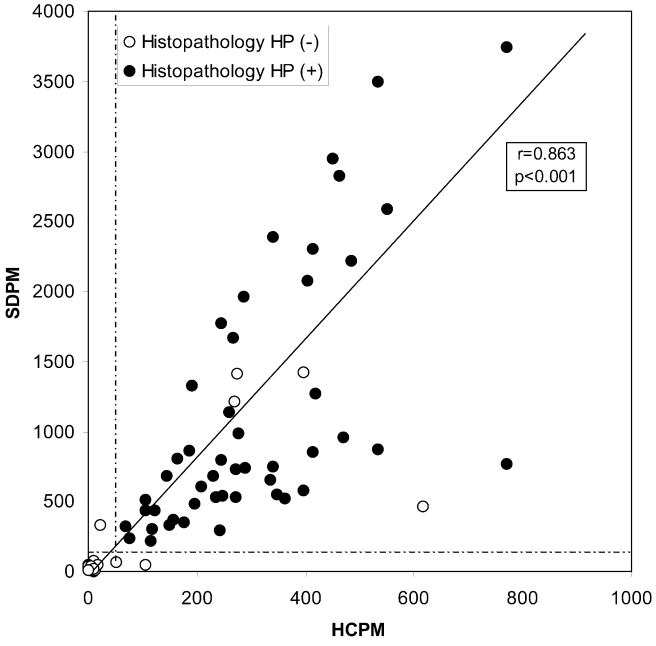

Fig. 1. Comparison of SDPM and HCPM

Results

Two patients were excluded from the study because of inadequate biopsy sampling. On histology, 48 patients (65%) were found to be HP positive, and 25 HP negative.

CLO test

Among the 48 patients evaluated with CLO test, 26 of 32 HP-positive (sensitivity 81% and PPV 86%) and 12 of 16 HP-negative patients (specificity 75% and NPV 66%) were correctly identified. Accuracy was 79% (Tables 1 and 2).

Heliprobe and standard methods

Table 3 shows the spread of the counts with both methods. Counts allowed clear discrimination of HP-positive and -negative patients with both methods, the difference being statistically significant in each case ($P<0.001$).

The Heliprobe method correctly classified 48 of 48 HP-positive patients and 19 of 25 HP-negative patients (sensitivity 100%, specificity 76%). The standard method correctly classified 48 of 48 HP-positive patients and 20 of 25 HP-negative patients (sensitivity 100%, specificity 80%) (Tables 1 and 2).

According to the grading with the Heliprobe method, all of the positive results were grade 2 (infected) and all of the negative results were grade 0 (not infected). No patients were defined as having grade 1 (equivocal) results.

Heliprobe method versus standard method

A significant correlation was found between HCPM and SDPM counts (r 0.863, $P<0.001$, Fig. 1). According to the ROC analysis, the area under the curve was nearly the same with HCPM (AUC, 0.888; 95% CI, 0.785–0.992) and SDPM (AUC, 0.898; 95% CI, 0.802–0.994) (Fig. 2).

Three HP-negative patients showed discordant results with the standard and Heliprobe methods. Two of them had positive test results only with the Heliprobe method (pt. 6: HCPM 105, SDPM 52; pt. 8: HCPM 52, SDPM 22), whereas one of them was positive only with the standard method (pt. 4: SDPM 330, HCPM 21).

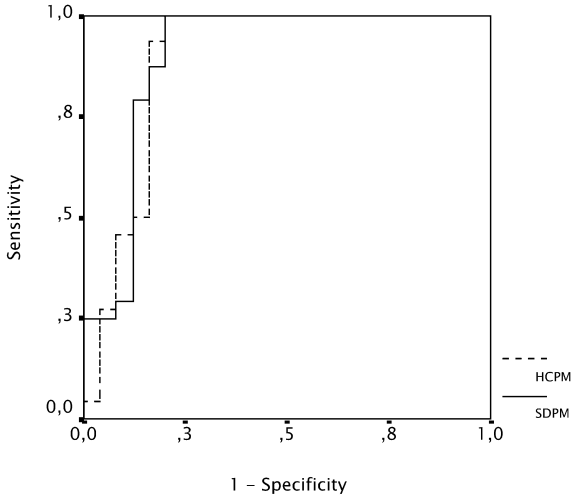

Fig. 2. ROC curve analysis of HCPM and SDPM

Discussion

This study shows that the new, practical Heliprobe ^{14}C-UBT system is highly accurate for the diagnosis of HP infection. Results obtained using the Heliprobe method are comparable to those using standard method [6, 7, 8], and a strong correlation between the methods was found in the present study.

Five patients with the standard method and six with the Heliprobe method had positive results despite negative histology. Since we validated our results against histology, these results were classified as false positive. But owing to the patchy distribution of HP in gastric mucosa, the biopsy-based tests may suffer from sampling error [10,11]. Furthermore, histological examination is highly dependent on the experience of the pathologist, and high inter-observer variation has been reported [11, 12]. Thus, it is likely that these patients were HP positive despite a negative histology. Sources of urease other than HP, such as bacterial overgrowth in the oropharynx, stomach or upper intestine, may rarely cause false-positive test results [6]. However, the reason for differences between the methods is not clear. Capsule dissolution may be slower in some patients, causing relatively lower radioactivity in early breath samples. If this is the case, Heliprobe breath samples may contain lower activity than standard samples, giving rise to a Heliprobe-negative, standard method-positive result.

The CLO test had low sensitivity and specificity in this study. Besides suffering from biopsy sampling error, the CLO test depends greatly on the pH of the media and the amount of the urea in the medium. These factors may vary in different products and thereby influence the results obtained with other tests [5, 10].

Various factors affect the results of the UBT. Several different methodological approaches have been suggested in order to simplify and increase the accuracy of the UBT. The differences concern doses and forms of ^{14}C-urea, patient preparation before the test, the time and number of breath samples, and modes of quantification. Our results showed that most of these steps can be omitted without prejudicing accuracy.

The original ^{14}C-UBT system used relatively high activities (200–400 kBq) and multiple breath sampling. Later studies showed that the diagnostic accuracy of ^{14}C UBT is maintained even with low doses and single breath samples [6, 7].

The UBT indirectly detects gastric HP by measuring urease activity. However, urease-producing bacteria are also present in the oropharynx and may cause false-positive results, especially in early breath samples. Late breath sampling may result in false-negative results because of emptying of urea from the stomach. Several procedures to avoid contamination of breath by the oropharyngeal flora have been suggested, including mouth washing, simultaneous meal to delay gastric emptying, and performance of multiple breath sampling. Another more simple and effective method is use of ^{14}C-urea in a gelatin capsule, thus bypassing the oropharynx. Hamlet et al reported that when the ^{14}C-urea is supplied in a capsule, a single 10-min breath sample is highly accurate (100% sensitivity and specificity) for the diagnosis of HP infection. They compared the capsule method with the urea drink method and found the former to be more reliable because no overlapping in activity occurred between HP-positive and -negative patients; by contrast, conventional breath testing showed overlapping during the whole 30-min test period. Their study also showed that a fatty test meal lowers the $^{14}CO_2$ excretion during the first 20 min and may adversely affect the accuracy of a rapid UBT [8]. Other advantages of the capsule form include commercial availability, no risk of spills, shorter test duration and a lower radiation dose.

The expression of results of UBT varies between investigators. Henze et al. and Veldhuyzen van Zanten et al. have used CPM [14, 15]. Because CPM is affected by chemical or colour quenching, chemical changes of the cocktail and methods of sample preparation, Pathak et al. strongly suggested the use of DPM counts [16]. For these reasons we preferred to use DPM counts in the standard method.

Some authors have used formulas to correct for body weight or body surface to account for differences in endogenous CO_2 production, the results being expressed as recovery standard units [(% of administered dose recovered/mmol CO_2 trapped) × body weight (kg)] [1, 7]. However, neither of these factors has been proved to influence the results of the breath test. Indeed, it has even been reported that uncorrected counts result in better distinction between HP-positive and -negative patients [8, 15, 16]. For this reason and to simplify the test, we omitted all such calculations. Both tests gave excellent results and a high correlation was found between DPM values

of the standard method and CPM values of the Heliprobe method.

Adequate patient preparation is important if accurate results are to be obtained with ^{14}C-UBT. A large number of investigators have reported that the UBT becomes false negative during therapy with proton pump inhibitors, lansoprazole, bismuth compounds, antibiotics and ranitidine [17, 18, 19]. Preliminary reports indicate that addition of citric acid to the urea solution/capsule may diminish the negative effect of acid-inhibitory drugs on the accuracy of UBT [20]. Although we used an acidified ^{14}C-urea capsule, we preferred to discontinue medications before the test for a certain period of time. The exact value of acidified urea needs further verification.

The dry, practical and ready-to-use breath cartridge is an important advantage of this new system. Besides the simple and easy collection of breath, this system prevents accidental ingestion of hazardous organic CO_2 absorber solutions during breath sampling.

Carbon-13 is a non-radioactive isotope, but ^{13}C-UBT is more expensive because it requires mass spectrometry. ^{14}C has a physical half-life of about 5,000 years, raising the question of the risks of radiation exposure. Because nearly the entire ingested isotope is rapidly excreted in urine or breath over the following 72 h and only a small amount of isotope is used, the test actually entails low radiation exposure (3 μSv) [21, 22]. In fact, the dose is less than the natural background radiation in one day. As mentioned by Boivin et al., the debate on safety has revolved only around the radiation dose received from ^{14}C-UBT, and it has been generally accepted that there is no or a lower risk with the ^{13}C alternative. On the other hand, ^{13}C-UBT contains more than 30,000 times as much urea as ^{14}C-UBT, and the safety of this amount of urea is also questionable [23]. For this reason, in 1997 the Nuclear Regulatory Commission permitted in vivo diagnostic use of capsules containing 1 μCi of ^{14}C-urea without a license [24].

Additional advantages of the Heliprobe system are the shorter test time and the low cost. Breath samples are analysed with a β-scintillation counter in ^{14}C-UBT and with a mass spectrometer in ^{13}C-UBT. Because both items of equipment are expensive, analysis can be done in an external laboratory by mail order and results are usually obtained a few days later. In contrast, with the Heliprobe system the results are obtained in half an hour on-site and the analyser is much cheaper than either a β-scintillation counter or a mass spectrometer.

In conclusion, the new Heliprobe ^{14}C-UBT is a simple, rapid, practical, safe, cheap and highly accurate system for the diagnosis of HP infection. The main advantages of the system are commercial availability, no risk of spills, reduced interference by oropharyngeal flora, shorter test duration, low radiation dose, simple and safe breath collection, and a practical and cheap counting system.

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