Evaluation of a novel ^{14}C-urea breath test "Heliprobe" in diagnosis of *Helicobacter pylori* infection

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Key words: *Helicobacter pylori; ^{14}C-urea breath test.*

Summary. *Background. At present, ^{14}C-urea breath test is considered a gold standard for diagnosis of Helicobacter pylori infection, but they are time-consuming, comparably expensive, and usually not portable tests. The aim of our study was to establish the diagnostic value of the novel, inexpensive, quick, and convenient to use ^{14}C-urea breath test "Heliprobe", Noster AB, Sweden.*

Material and methods. Helicobacter pylori testing using "Heliprobe" was performed in 108 consecutive patients. Helicobacter pylori was also investigated using rapid urease test and Giemsa stained histological specimens according to Sydney system.

Results. The diagnostic values of "Heliprobe" assuming the Helicobacter pylori positivity, if the results of two tests (rapid urease test and histology) are positive, were: sensitivity – 97%, specificity – 87%, positive predictive value – 93%, negative predictive value – 95%, accuracy – 94%. The diagnostic values of "Heliprobe" assuming the Helicobacter pylori positivity, if at least the results of one test are positive: sensitivity – 92%, specificity – 100%, positive predictive value – 100%, negative predictive value – 84%, accuracy – 94%.

Conclusions. The novel, quick, convenient to use ^{14}C-urea breath test "Heliprobe" is accurate, reliable, and useful for the diagnosis of Helicobacter pylori infection in routine clinical practice.

Introduction

Since the discovery of *Helicobacter pylori* (HP) infection (1), a huge amount of research has been carried out to define the role of this microorganism in the gastroduodenal pathology (2). A lot of diagnostic tests to determine HP infection have been confirmed as reliable testing tools (3). However, some problematic issues remain, because under certain conditions the results of tests can be "false positive" or "false negative" (4). At present, urea breath test (UBT) is considered a gold standard for diagnosis of HP infection (5). There are two carbon isotopes used for UBT: ^{13}C – not radioactive, and ^{14}C – radioactive. ^{13}C-UBT is not invasive, highly accurate, but time consuming, comparably expensive, and usually not portable (6). These inconveniences could be somehow accepted in the economically developed Western Europe and North America countries. But in the developing African, Asian, Eastern European, and other countries, where prevalence of HP is high, there is an urgent need for accurate, inexpensive, and rapid urea breath tests (7). In these countries, up until recently, the most cheap and accepted diagnostic tool remains rapid urease test (RUT), which is invasive and related to the complications of endoscopy.

Therefore, the search for better diagnostic tool in high HP prevalence regions is going on. The Swedish company Noster AB created a new ^{14}C-based urea breath test "Heliprobe," which is portable and easy to use, and diagnosis of HP can be made in 20 minutes. Tests are comparably inexpensive. The radioactivity of C^{14}-based urea capsule is extremely low and is practically comparable to natural radiation.

"Heliprobe" was recently validated against conventional ^{14}C-UBT. It was concluded that "Heliprobe" is equiefficacious to conventional UBT in fulfilling its role as the noninvasive gold standard for detection of HP (8). However, until now there are no data published about comparison of this test to widely used rapid urease test and histological staining in high HP prevalence areas.

The aim of our study was to establish the sensitivity, specificity, positive and negative predictive values of the new ^{14}C-urea breath test (^{14}C-UBT "Heliprobe", Noster AB, Sweden) and to evaluate its usefulness in diagnosing HP infection in routine clinical practice.

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Methods

The new "Heliprobe" UBT is a completely dry system consisting of two components, the *Heliprobe BreathCardTM* and the *Heliprobe AnalyzerTM*. The *Heliprobe BreathCard* is a flat, credit-card-sized collection device that adsorbs exhaled CO_2 via chemical bounding to pads soaked in LiOH. Ten-fifteen minutes after ingestion of small capsule with ^{14}C-urea, the collection process is performed: the patient breathes into a mouthpiece on the card until a pH-sensitive indicator changes color from orange to yellow as an indication of CO_2 saturation of the pads. The breathing time varies depending on the number of breaths into the card, the average time being approximately 1–2 min. Since the exhaled CO_2 is bound chemically to the pads, the card can be stored for several years without loss or deterioration of its CO_2 content. With the *Heliprobe Analyzer*, the traditionally used liquid β-scintillator has been replaced with an instrument containing two built-in Geiger-Muller counters operating in parallel. This technology swap has made it possible to design a cheap, small (laptop-sized), and fully automatic analyzer that can be operated by the nurse or physician in a clinic. The *Heliprobe BreathCard* is simply put into the slot of the *Heliprobe Analyzer*. By pressing the start button, a fully automatic test sequence is initiated and runs for 250 s. The result of the measurement is presented on a liquid-crystal display and on a printer. The analysis is based on the number of emitted β-particles that hit the two Geiger-Muller counters during a 250-s measurement cycle, and values are presented as counts per min (cpm) together with the test result "negative," "equivocal," or "positive." The cutoff levels between the different test results are based on the obtained cpm values. The diagnostic cutoff is programmable to different levels by setting lower and upper limits. A cpm value below the lower limit is presented as a negative result, values between the lower and upper limits are presented as equivocal, and values above the upper limit are positive. By setting the lower and upper limits to the same value, equivocal results can be avoided. The *Heliprobe Analyze* is continuously compensating for background radioactive variations, thereby eliminating this source of error.

HP was also investigated using RUT and Giemsa-stained histologic specimens according to Sydney system (9). For RUT, we used two biopsies (one from antrum and one from corpus of the stomach). For histologic diagnosis, two biopsies from antrum and two biopsies from the corpus of the stomach were obtained. A single pathologist who was blinded to other patient's data evaluated histologic specimens.

The Ethics Committee of Kaunas University of Medicine approved the study.

Statistics. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new C^{14}-UBT assuming two possibilities:

1) The "gold standard" for HP-positivity is if the results of both tests (RUT and histology) are positive.
2) The "gold standard" for HP-positivity is if the results of one test (RUT or histology) are positive.

Results

HP testing was performed in 108 consecutive patients who had not been using proton pump inhibitors, bismuth compounds, antibiotics, and nonsteroidal antiinflammatory drugs for at least one month before testing. The mean age of our patients was 42.0±12.3 years. There were 70 (64.8%) women and 38 (35.2%) men.

The results of C^{14}-UBT were positive in 71 (65.7%) cases, negative – in 37 (34.3%) cases. The evaluations of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the test are presented in Table.

Table. **Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the "Heliprobe"**

Characteristic	HP positivity if results of two* reference tests are positive	HP positivity if results of at least one** of reference tests are positive
Sensitivity, %	97	92
Specificity, %	87	100
PPV, %	93	100
NPV, %	95	84
Accuracy, %	94	94

* Results of both reference tests are positive: rapid urease test and histology.
** Results of one of reference tests (rapid urease test or histology) are positive.

Discussion

Our data revealed that novel ^{14}C-UBT "Heliprobe" has an excellent diagnostic accuracy comparing it with very widely used HP testing modalities – RUT and histological staining. The overall accuracy of the test was 94%, what corresponds with elsewhere-reported accuracies of conventional UBT and with accuracies of other frequently applied invasive and noninvasive HP diagnostic tools (10).

The advantages of "Heliprobe" are noninvasiveness, rapidness, "easiness to perform," possibility of storage, possibility to use in almost any conditions (close to patient's bedside), and inexpensiveness. Therefore, this test could be very important diagnostic tool in the high HP prevalence areas, where it will take long period to get rid of HP. According to already published data, "Heliprobe" is equally accurate before the treatment and after eradication of HP. Accurate determination of HP is very important in the developing countries, where the results of widely used RUT and histological staining are infrequently "false negative." This leads to recrudescence of HP and further progression of HP-related gastroduodenal pathology.

Some may speculate that the radioactivity is disadvantage of ^{14}C-UBT "Heliprobe" as of other ^{14}C-UBTs. In the ^{14}C-UBT, urea either undergoes hydrolysis, being exhaled as $^{14}C\ O_2$, or is eliminated unchanged in urine. Because the biological half-life of urea is short, the cumulated radiation dose from each breath test is small and far below variations in natural radiation. According to data reported by D. J. Munster *et al.* (11), approximately 90% of the ^{14}C from a UBT is eliminated as CO_2 in breath or as urea in urine. This would mean that after 3 days, the amount of isotope retained in the body is negligible. The cumulative lifetime radiation exposure from this test has been calculated to be not more than 0.3 mrem/μCi, which is considered equal to the background radiation a person is exposed to in 1 day (12, 13). Due to very low level of radioactive exposure, the 1-μCi ^{14}C dose has been permitted for general use in UBTs in the USA (Nuclear Radioactive Committee, USA, 10CFR § 30.21 Radioactive drug: Capsules containing carbon-14 urea for diagnostic use in humans). We therefore consider the radioactive burden on each person to be very limited, even not precluding repeated tests in the same person. Some reports even conclude that there is no reason for restrictions on repeated investigations with ^{14}C-urea in whole families, including children (14).

In the paper by W. D. Chey, it was noted that the inexpensive ^{14}C-urea breath test provides an attractive, noninvasive means of identifying active HP infection (15). Accurate, with very low radioactivity, and inexpensive ^{14}C-based urea breath test started also to be refined in Scandinavian countries (16). Therefore, it seems very likely to start to use them in every day's activities of small hospitals and primary care offices.

The new convenient ^{14}C-UBT "Heliprobe" is a reliable and useful tool in diagnosing HP infection in routine clinical practice.

^{14}C šlapalo kvėpavimo testo „Heliprobe" įvertinimas diagnozuojant *Helicobacter pylori* infekciją

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Raktažodžiai: *Helicobacter pylori*, ^{14}C šlapalo kvėpavimo testas.

Santrauka. Šlapalo kvėpavimo testai laikomi *Helicobacter pylori* infekcijos nustatymo „auksiniu standartu". Deja, Lietuvoje šie testai dar nenaudojami, nes ^{13}C šlapalo kvėpavimo testui skirta spektrometrinė technika labai brangi, todėl mes pirmieji Lietuvoje siekėme ištirti greito ir patogaus naudoti ^{14}C šlapalo kvėpavimo testo diagnostinį tikslumą palyginti su iki šiol naudojamais testais.

Metodai. Helicobacter pylori tyrimas, naudojant „Heliprobe" (Noster AB, Švedija) ^{14}C šlapalo kvėpavimo testą, atliktas 108 ligoniams. *Helicobacter pylori* buvo tiriama naudojant ir greitą ureazės testą ir histologinį tyrimą (pagal pripažintą Sidnėjaus sistemą).

Rezultatai. Jei laikėme, kad *Helicobacter pylori* nustatyta, kai abu įprasti tyrimo metodai buvo teigiami, ^{14}C šlapalo kvėpavimo testo diagnostiniai parametrai buvo: jautrumas – 97 proc., specifiškumas – 87 proc., teigiama prognostinė vertė – 93 proc., neigiama prognostinė vertė – 95 proc., tikslumas – 94 proc.

Jei laikėme, kad *Helicobacter pylori* nustatyta, kai bent vienas iš įprastų tyrimo metodų buvo teigiamas, ^{14}C šlapalo kvėpavimo testo diagnostiniai parametrai buvo: jautrumas – 92 proc., specifiškumas – 100 proc.,

teigiama prognostinė vertė – 100 proc., neigiama prognostinė vertė – 84 proc., tikslumas – 94 proc.

Išvados. Naujasis greitas ir patogus naudoti ^{14}C šlapalo kvėpavimo testas „Heliprobe“ yra tikslus ir informatyvus metodas *Helicobacter pylori* infekcijai nustatyti kasdienėje klinikinėje praktikoje.

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References

1. Marshall B, Warren R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311-4.
2. Kuipers EJ, Uyterlinde AM, Pena AS, Roosendaal R, Pals G, Nelis GF, et al. Long term sequelae of *Helicobacter pylori* gastritis. Lancet 1995;345:1525-8.
3. Braden B, Caspary WF. Detection of *Helicobacter pylori* infection: when to perform which test? Ann Med 2001;33: 91-7.
4. De Boer WA. Diagnosis of *Helicobacter pylori* infection. Review of diagnostic techniques and recommendations for their use in different clinical settings. Scand J Gastroenterol 1997;223:35-42.
5. Logan RP. Urea breath tests in the management of *Helicobacter pylori* infection. Gut 1998;43:S47–S50.
6. Parente F, Bianchi Porro G. The (13)C-urea breath test for non-invasive diagnosis of *Helicobacter pylori* infection: which procedure and which measuring equipment? Eur J Gastroenterol Hepatol 2001;13:803-6.
7. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. Aliment Pharmacol Ther 1995; 9:33-9.
8. Hegedus O, Ryden J, Rehnberg AS, Nilsson S, Hellstrom PM. Validated accuracy of a novel urea breath test for rapid *Helicobacter pylori* detection and in-office analysis. Eur J Gastroenterol Hepatol 2002;14:1-8.
9. Dixon MF, Genta M, Hardley JI, and participants in the international workshop on the histopathology of gastritis. Houston 1994. Classification and grading of gastritis: the updated Sydney System. Am J Surg Pathol 1996;20:1161-81.
10. Vaira D, Gatta L, Ricci C, Miglioli M. Review article: diagnosis of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2002;16:16-23.
11. Munster DJ, Chapman BA, Burt MJ, Dobbs BR, Allardyce RA, Bagshaw PF, et al. The fate of ingested 14C-urea in the urea breath test for *Helicobacter pylori* infection. Scand J Gastroenterol 1993;28:661-6.
12. Stubbs JB, Marshall BJ. Radiation dose estimates for the carbon-14-labeled urea breath test. J Nucl Med 1993;34:821-5.
13. Goddard AF, Logan RP. Urea breath tests for detecting *Helicobacter pylori*. Aliment Pharmacol Ther 1997;11:641-9.
14. Leide-Svegborn S, Stenstrom K, Olofsson M, Mattsson S, Nilsson LE, Nosslin B, et al. Biokinetics and radiation doses for carbon-14 urea in adults and children undergoing *Helicobacter pylori* breath test. Eur J Nucl Med 1999;26:573-80.
15. Chey WD. Accurate diagnosis of *Helicobacter pylori*. 14C-urea breath test. Gastroenterol Clin North Am 2000;29:895-902.
16. Rehnberg AS, Bengtsson C, Befrits R, Granstrom M, Hellstrom PM. Refinement of the 14C-urea breath test for detection of *Helicobacter pylori*. Scand J Gastroenterol 2001;36:822-6.

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