

Comparison of the C14 urea breath test and histopathology in the diagnosis of helicobacter pylori in the elderly

Teslime Atli,¹ Sevnaz Sahin,² Bilge Ugur Arslan,³ Murat Varli,⁴ Ahmet Emre Yalcin,⁵ Sevgi Aras⁶

Department of Internal Medicine, Division of Geriatrics, Medical Faculty, Ankara University,^{1,3-6}

Department of Internal Medicine, Division of Geriatrics, Medical Faculty, Ege University,² Ankara, Turkey.

Corresponding Author: Sevnaz Sahin. Email: drsevnaz@hotmail.com

Abstract

Objectives: To compare the sensitivity and specificity of C[14] urea breath test with histopathological findings in biopsies obtained through endoscopy.

Methods: In this cross-sectional study, conducted at the Medical Faculty Ankara University, Ankara, Turkey between January and October 2009, 100 patients aged 65 and above who fulfilled the criteria for inclusion were enrolled. Oesophago-gastroduodenoscopy was carried out on the patients after eight hours of fasting, using a Fujinon endoscope, by the same expert. C¹⁴ urea breath tests were carried out on all patients with a capsule containing 37 kBq(1μ Ci) C¹⁴ urea/citric acid. Evaluation of all data was carried out using SPSS 11.5. Categorical variables were compared through Pearson Chi squared or Fisher's exact test. P<0.005 was taken as statistically significant.

Results: The average age of the patients was 71 ± 5 years; 43 (43%) were male; and 57 (57%) were female. Helicobacter pylori positivity was found to be 35 (35%) in histopathological evaluation, and 36 (36%) in the C¹⁴ urea breath test. Of the 35 patients, 32 (91.4%) were found to be positive by the C¹⁴ urea breath test also. Of the 65 patients who were found to be negative on histopathology, 61 (93.8%) were also found to be Hp negative by the C¹⁴ urea breath test, and 4 (6.2%) were evaluated as false positive. A statistically significant correlation (p<0.001) was found between histopathological and C¹⁴ urea breath test results. Compared with histopathology, the sensitivity of the urea breath test was 91.4%, and its specificity was 93.8%. A statistically significant (p <0.001) relationship was found between histopathological results and the results of the C¹⁴ urea breath test.

Conclusion: The sensitivity and specificity of the C[14] urea breath test in the group of elderly patients selected was high. The C¹⁴ urea breath test can be considered in the elderly group for diagnosis of Helicobacter pylori infection.

Keywords: Urea breath test, Histopathological, Helicobacter pylori infection. (JPMA 62: 1061; 2012)

Introduction

The association between stomach illnesses and *Helicobacter pylori* (Hp) was first demonstrated in 1983, and today it is accepted as the most widespread chronic infection known.^{1,2} Infection levels vary from country to country, but the global average rate of Hp infection is estimated to be 50%.³ The prevalence of Hp in elderly people is greater than in young people, and is reported to be over 70%.⁴ Hp infection plays an important role in the pathogenesis of chronic gastritis, gastro duodenal ulcers, and structural and functional diseases of the duodenum. A 2 to 6-fold increase in the development of gastric malignancies and Mucosa-Associated Lymphoid Type (MALT) lymphoma is found in people infected with Hp.⁵ In 1994, the International Agency for Research on Cancer (IARC), part of the World Health Organisation, announced that Hp was carcinogenic in humans.⁶

One of the suggestions of the Maastricht III report of the European study group on Hp is the test and treatment strategy for unverified patients under the age of 45 with persistent dyspepsia.⁷ By using non-invasive examination in testing and treating the selected group of patients, the need for endoscopy is appreciably reduced.

The identification of Hp infection by suitably easy, quick and direct methods is important in the treatment and the verification of treatment. At present, both invasive and non-invasive methods are used in the diagnosis of Hp. There is no consensus on the most appropriate method in diagnosis of infection by Hp in literature. Invasive methods include identification of the agent by histopathology in samples taken from the stomach mucosa, a fast urease test, polymerase chain reaction (PCR), and culture methods. Non-invasive methods are the urea breath test, serological tests, and detection of Hp antigen in the stool. There is no gold standard for diagnosis, and some combination of both methods is generally chosen according to the preferences or the patient's features or the facilities available.⁸ Correct diagnosis rates of 80-84% are reported for non-invasive tests by the serological method, but it should not be forgotten that tests may be positive for 6-12 months after eradication, and this does not indicate active infection. The necessity of storing samples at -20° in the stool Hp antigen method limits its practical application. The other non-invasive test is the urea breath test, which, because of its 97-100% sensitivity and 95-100% specificity found in various studies, is the method which is the most recommended.^{9,10}

With increasing age, the prevalence of Hp increases.¹¹ In Turkey, although there have been studies on the frequency of Hp in children and young adults, but data on the population of over-65s is insufficient. In spite of its high prevalence among old people, they receive treatment and followup for Hp less frequently than young patients.^{12,13}

The aim of this study was to compare the sensitivity and specificity of the C14 urea breath test with histopathological findings in biopsies obtained through endoscopy in people aged 65 and above.

Patients and Methods

This cross-sectional study, conducted at Medical Faculty, Ankara University, Ankara, Turkey, between January and October 2009, included 100 patients aged 65 years and above, for whom endoscopy was planned and who conformed to the inclusion criteria. Criteria for inclusion comprised complaints of dyspepsia (epigastric pain, distension and vomiting unconnected with eating), symptoms of a suspected peptic ulcer, gastro-oesophageal symptoms, and planned endoscopy because of iron deficiency and/or vitamin B12 deficiency. Patients were excluded from the study if they were using antibiotics in the preceding two weeks, using H2 receptor blockers and/or proton pump inhibitors, having advanced dementia, cerebrovascular disease, advanced respiratory problems and alarm symptoms for malignancy. All patients were asked whether they smoked.

Oesophago-gastroduodenoscopy was carried out on the patients after eight hours of fasting, using a Fujinon endoscope, by the same expert. Before the operation, local pharyngeal anaesthesia was applied with xylocain. At least four biopsy samples were taken for histopathological evaluation from different regions of the antrum and corpus of the stomach.

After at least six hours of fasting, all patients were given a capsule containing 37 kBq (1 µ Ci) C14 urea/citric acid to drink in 25ml of water. Ten minutes after having taken the capsule, the patient blew into the heliprobe cartridge until the pH indicator turned from orange to yellow. C14 activity in the cartridge was measured for 250 seconds with the Heliprobe analyser; >50 cpm was taken as positive; 25-50 cpm as suspicious; and <25 cpm as negative.

Before the study, benefits and risks of the procedures were explained to the patients and an informed consent form was signed by all the patients.

For statistical analysis, SPSS 11.5 was used. Descriptive statistics were expressed as mean ± standard deviation, and nominal continuous variables were reported as frequencies and percentages. Categorical variables were compared by means of Pearson Chi square or Fisher's exact test. Results were accepted as statistically significant at $p < 0.005$.

Results

The average age of patients included in the study was 71 ± 5 years; 43 (43%) were male, and 57 (57%) were female. Of the 35 (35%) patients who were found to be Hp positive, there were 19 (54.3%) women, and 16 (45.7%) men. No statistically significant difference between the genders was found for Hp

Table-1: Symptoms in Hp+, Hp-, and all patients.

Complaint	Hp (+) (n=35)	Hp (-) (n=65)	Total (n=100)
Dyspepsia	23 (65.7%)	32 (49.2%)	55 (55%)
Gastro-oesophageal reflux	7 (20%)	14 (21.5%)	21 (21%)
No complaint	3 (8.6%)	12 (18.5%)	15 (15%)
Peptic ulcer	2 (5.7%)	7 (10.8%)	9 (9%)

Hp: Helicobacter pylori.

Table-2: Comparison of the urea breath test with histopathological Hp results.

Urea breath test	Histopathology		P
	Hp (+) (n=35)	Hp (-) (n=65)	
Negative	3 (8.6%)	61 (93.8%)	p<0.001
Positive	32 (91.4%)	4 (6.2%)	p<0.001

positivity (p>0.05).

Eleven (34.4%) of the 32 patients who smoked and 24 (35.3%) of the 68 who did not smoke were found to be Hp positive. No statistically significant relationship was found between the two groups (p>0.05).

When a comparison was made between the existence of Hp according to histopathology and symptoms, the most commonly observed symptom among Hp positive patients was dyspepsia (n=23; 65.7%), followed by gastro-oesophageal reflux (n=7; 20%) (Table-1).

According to endoscopy, most of the patients had more than one pathology; 33 (33%) patients had antral gastritis, 31 (31%) had pangastritis, 27 (27%) had oesophagitis, 23 (23%) had erosive gastritis, 22 (22%) had duodenitis, 5 (5%) had a duodenal ulcer, 4 (4%) had chronic atrophic gastritis, and 2 (2%) had Barrett's oesophagus.

Hp positivity was found at a rate of 35 (35%) by histopathological examination, and at 36 (36%) by the C14 urea breath test; 32 (91.4%) of the 35 patients identified as Hp positive by histopathology were also found to be Hp positive by the C14 urea breath test. Of the 65 patients found to be Hp negative on histopathology, 61 (93.8%) were also found to be Hp negative by the C14 urea breath test, while four were found to be false positive.

A statistically significant relationship was found between the histopathology results and the results of the C14 urea breath test (p<0.01). In comparison with histopathology, the sensitivity of the urea breath test was 91.4% and its specificity was 93.8% (Table-2).

Discussion

The level of Hp positivity was found to be 35% by histopathology, and 36% by the C14 urea breath test. These Hp positivity levels were lower than those in the literature. The reason for this could be the high-profile socioeconomic level of

the region where the study was carried out, or because patients with gastro-oesophageal reflux were included in the study. In the literature it is stated that the prevalence of Hp in developed countries is low, and studies in Turkey support the assertion. At the same time it has been found that the level of Hp also increases with age. However, as our study did not include young adults, it was not possible to make a comparison of age groups. A study found that the level of Hp was lower in the population aged 65 and above than in other age groups, though the difference was not statistically significant.¹⁴ In Turkish studies using anti-Hp Immunoglobulin G (IgG), seroprevalence among adults varied from 70.1 to 85%, while in children it was between 20 and 66%.¹⁵⁻¹⁸ In a study by Özden et al. examining Hp seroprevalence in the preceding 10 years in children between seven and 14 years old, it was found that the rate of 78.5% in 1990 had fallen to 66.3% in 2000. This was ascribed to the improvement in environmental factors and socioeconomic conditions.¹⁹ In the literature and in most Turkish studies broad age groups, including those aged 65 and above, are limited. Since the patients included in our study were old, and most of them were attending the hospitals, it is not possible to generalise this prevalence, and further studies are needed in this area which shall include various age groups.

Consistent with the literature, no significant difference was found between the genders regarding the occurrence of Hp. Some publications assert that one of the multiple factors affecting the occurrence of Hp is smoking, but in the present study no significant association between smoking and Hp was found.^{14,20}

Examining the occurrence of Hp and symptoms, the most frequent symptom was dyspepsia, which was parallel to the endoscopic findings of gastritis (antral gastritis, pangastritis, erosive gastritis, and chronic atrophic gastritis). Hp positivity was found to be 65.7% in patients complaining of dyspepsia. No significant relationship was found between endoscopic findings and Hp.

Of the 35 patients who were found to be Hp positive histopathologically, 32 (91.4%) were Hp positive by the C14 urea breath test. Of the 65 patients who were found to be Hp negative by histopathology, 61 (93.8%) were also found to be Hp negative by the C14 urea breath test. In comparison with histopathology, the sensitivity of the urea breath test was found to be 91.4%, and its specificity was 93.8%.

Although there is not yet a mere gold standart for the diagnosis of Hp infection, but the highest sensitivity and specificity have been reported by the histopathologic assessment. In one study, the authors compared Rapid Urease Test (RUT), Touch Cytology (TC) and histopathologic assessment. The sensitivity, specificity, and accuracy of RUT, TC and histopathologic assessment were reported as 92.7, 60, 66.75; 100, 90 and 98%; and 95.1, 100 and 96.1% respectively.⁸

In the present study, a statistically significant relationship was found between histopathological Hp results and the results of the C14 urea breath test ($p < 0.001$).

The urea breath test is a non-invasive test which was recognised in 1987 and relies on the urease activity of the bacteria. It relies on the principle of the conversion of urea into Nitrogen trihydride (NH₃) and carbon dioxide (CO₂) by the urease enzyme. Urea marked by C¹³ and C¹⁴ is hydrolysed to NH₃ and CO₂ by Hp in the stomach and labelled isotopes of carbon in the CO₂ exhaled by the lungs is measured. The greatest advantage of the urea breath test is that it samples the whole stomach, thus avoiding problems which can arise with invasive tests such as biopsy because of the fact that the bacteria can be distributed patchily on the stomach mucosa. Urea can be marked with two different isotopes; C¹³ which is stable, and C¹⁴ which is radioactive. The use of C¹³ at different doses in the diagnosis and followup of Hp has shown a sensitivity of 89.1-100% and a specificity of 100%.⁹ The cost of the equipment and isotope needed for the urea breath test with C¹³ is high compared to the C¹⁴ isotope.²¹ One of the strong points of our study was that it used the isotope C¹⁴, which is cheaper and easier to use.

The guidelines on the management of dyspepsia recommend that non-invasive methods should be used for diagnosis and treatment.^{22,23} Invasive methods involve difficulties of application in aged patients because of the risk of co-morbid diseases, so that non-invasive methods must be preferred in this group of patients. It was found in this study that the sensitivity and specificity of the urea breath test was high in aged patients as it is in the young patients. For this reason we are of the opinion that the urea breath test is suitable for use in testing for the existence of Hp in old patients who have not previously received treatment and who do not have the alarm symptoms suggesting malignancy. A limitation of our study is that the response of patients who were Hp positive and who

were receiving treatment was not re-evaluated by the urea breath test.

In one study, authors found that the urea breath test could also be used in the followup of Hp eradication in the young population.²⁴ Data on this topic in aged patients is limited: it was found in a study comprising 140 patients with an average age of 68.6 ± 5.4 that the urea breath test was effective in followup treatment.²⁵

Studies comparing the evaluation of the diagnostic sensitivity and specificity of the urea breath test in aged patients are limited. The results of our study are important in that they show that a non-invasive test which is easy to apply and can be used in place of invasive methods. And because it is inexpensive and easy to access, the C¹⁴ urea breath test may be the preferred non-invasive test.

Conclusion

The sensitivity and specificity of non-invasive methods for the diagnosis of Hp in the group of elderly patients selected was high. The C¹⁴ urea breath test can be considered in the elderly group for diagnosis of Hp infection. The ease of application and cost-effectiveness of the non-invasive C¹⁴ urea breath test should also be kept in mind. There is a need for studies to be carried out on a larger group of patients to establish the effectiveness of the urea breath test in the diagnosis of Hp in aged patients.

References

1. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; 1: 1273-5.
2. Cave DR. Transmission and epidemiology of *Helicobacter pylori*. *Am J Med* 1996;100 (Suppl 5A): 12-7.
3. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Thera* 1995; 9 (Suppl 2): 33-9.
4. Pilotto A. Aging and the gastrointestinal tract. *Ital J Gastroenterol Hepatol* 1999; 31: 137-53.
5. Sipponen P, Hyvarinen H. Role of *Helicobacter pylori* in the pathogenesis of gastritis, peptic ulcer and gastric cancer. *Scand J Gastroenterol* 1993; 28 (Suppl 196): 3-6.
6. Anonymous. Live flukes and *Helicobacter pylori*. IARC Working Group on the evaluation of carcinogenic risks to Humans. Lyon 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; 61: 1-241.
7. Malfertheiner P, Megraud F, O Morain C, Bazzolini F, El Omer E, Graham D, et al. Current concepts in the management of the *Helicobacter pylori* infection: the Maastricht III consensus report. *Gut* 2007; 56: 772-81.
8. Fakhrjoui A, Somi MH, Fattahi E, Koohbanani SS and Shadravan S. Rapid Urease Test, Touch Cytology and histopathologic assessment in determining infection by *Helicobacter pylori* in outpatients setting. *Pak J Biol Sci* 2011; 14: 698-702.
9. Ahuja V, Bal CS, Sharma MP. Can the C-14 urea breath test replace followup endoscopic biopsies in patients treated for *Helicobacter pylori* infection? *Clin Nucl Med* 1998; 23: 815-9.
10. Gatta L, Ricci C, Tampieri A, Osborn J, Perna F, Bernabucci V et al. Accuracy of breath tests using low doses of 13 C-urea to diagnose *Helicobacter pylori* infection: a randomised controlled trial. *Gut* 2006; 55: 457-62.
11. Pilotto A, Malfertheiner P. An approach to *Helicobacter pylori* infection in the elderly. *Aliment Pharmacol Ther* 2002; 16: 683-91.
12. Roll J Weng A, Newman J. Daignosis and treatment of *Helicobacter pylori* infection among California Medicare patients. *Arch Intern Med* 1997; 157: 994-8.
13. Ofman JJ, Etchason J, Alexander W, Steven BR, Herrin J, Cangialose C et al. The

- quality of care for Medicare patients with peptic ulcer disease. *Am J Gastroenterol* 2000; 95: 1110-1111.
14. Marakoglu K, Eke AA, Civi S. Smoking as an important factor increasing risk of *Helicobacter pylori*. *Turk J Gastroenterol* 2008; 19: 133-41.
 15. Alim A, Atas AD, Günes T, Atas M, Yildirim M, Oztekin A et al. Seroprevalance of *Helicobacter pylori* in Asymptomatic and Syptomatic Adults Individuals in Sivas City Centre. *C.U. Tip Fakultesi Dergisi Dergisi* 2004; 26: 75-80.
 16. Altindis M. Seroprevalance of *Helicobacter pylori* infection in Afyon region. *Genel Tip Dergisi* 2001; 11: 109-12.
 17. Söğüt A, Acun C, Cavuldak S, Komsu Z, Tomaç N. Investigation of seropositivity and risk factors of *helicobacter Pylori* in children between 6 and 15 years in Zonguldak Türk Pediatri Arsivi 2004; 39: 152-7.
 18. Ceylan A, Kirimi E, Tuncer O, Türkdogan K, Ariyuca S, Ceylan N. Prevalance of *helicobacter pylori* in children and their family members in a district in Turkey. *J Health Popul Nutr* 2007; 25: 422-7.
 19. Özden A, Bozdayi G, Özkan M, Köse KS. Changes in the seroepidemiological pattern of *Helicobacter pylori* infection over the last 10 years in Turkey. *Turk J Gastroenterol* 2004; 15: 156-8.
 20. Meurer LN, Bower DJ. Management of *Helicobacter pylori*. *Am Fam Physician* 2002; 65: 1327-36.
 21. Parente F, Bianchi Poro G. The 13 C-urea breath test for non-invasive daignosis of *Helicobacter pylori* infection:which procedure and which measuring equipment ? *Eur J Gastroenterol Hepatol* 2001; 13: 803-6.
 22. Talley NJ, Vakil N. Practice Parameters Committee of the American College of Gastroenterology:guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; 100: 2324-37.
 23. Dyspepsia: Management dyspepsia in adults in primary care NICE guidelines. Published by the National Institute for Clinical Excellence. London, August 2004.
 24. Gatta L, Ricci C, Tampieri A, Osborn J, Perna F, Bernabucci Vet al Accuracy of breath tests using low doses of C13 urea to diagnose *Helicobacter pylori* infection: a randomised controlled trial *Gut* 2006; 55: 457-62.
 25. Rotolo G, Dominguez LJ, Sarakatsianou V, Mangiaracia D, Figlioli F, Barbagallo M. Test and treat strategy for *Helicobacter pylori* infection in older patients. *Archives Of Gerontology and Geriatrics* 2010; 51: 237-40.
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