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BRIEF ARTICLE

Detection of *Helicobacter pylori*: A faster urease test can save resources

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Abstract

AIM: To investigate whether differences in the rapidity of a positive result for *Helicobacter pylori* can save res ources, by comparing two commercially available urease kits.

METHODS: One hundred and eighty-five adults (130 outpatients, 55 inpatients) undergoing gastroscopy were entered prospectively. Patients were divided into two groups: Group 1 (if they were not on PPIs, antibiotics, H_2A, bismuth or sucralfate for up to 14 d prior to the endoscopy) and Group 2 (if they were on, or had been on, any of the above medication in the previous 14 d). At endoscopy two sets of biopsies, taken in random order, were placed in the wells of the *Campylobacter*-like organism (CLO) test (Kimberly-Clark, Utah, USA) and the Quick test (Biohit Plc, Helsinki, Finland). Five additional gastric biopsies were taken for histology/Giemsa and immunohistochemical study. The two urease test slides were read at 2 min, 30 min, 2 h and 24 h. Sensitivity and specificity at 24 h were determined.

RESULTS: At 24 h, for all patients, there was no difference in sensitivity (100% *vs* 97.5%), specificity (99.3%), positive (97.5%) and negative predictive values (100% *vs* 99.3%) between the CLO and Quick tests, respectively. There was a positive result at 30 min in 17/41 (41.5%) CLO tests, and in 28/40 (70%) Quick tests, $P = 0.05$. Quick test enabled the prescription of eradication therapy before discharge in all 28/40 patients. Only 12 (30%) follow-up appointments were needed. If the CLO test had been used alone, only 17 (41.5%) prescriptions would have been possible prior to discharge and 24 (58%) follow-up appointments would be needed ($P = 0.001$). Of 2000 gastroscopies performed annually at our unit, a saving of 123 follow-up appointments (total: 8856 Euros or 11 808 USD) would be achieved if we switched to the Quick test.

CONCLUSION: Direct comparison of locally available urease test kits is worthwhile, since the appropriate choice results in a significant saving of resources. Local costs and follow-up protocols will determine the magnitude of these savings.

Key words: *Campylobacter*-like organism test; Diagnosis; *Helicobacter pylori*; Quick test; Urease test kits

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped gram-negative bacterium which was identified in 1979[1]. It produces urease in abundance, the activity of which, through the production of ammonia, together with the bacterium's motility and ability to adhere to the gastric mucosa, enables its survival in the acid environment of the stomach. *H. pylori* is a causative agent for chronic active gastritis, peptic ulcer disease, gastric cancer and mucosa associated lymphoid tissue lymphoma[2]. It has also been shown to be associated with extragastric diseases, such as iron deficiency anemia and idiopathic thrombocytopenic purpura[3-5].

Non-invasive methods of *H. pylori* detection include serum antibody detection, fecal antigen tests[6] and the urea breath test[7]. Invasive methods of *H. pylori* detection require endoscopy in order to obtain gastric tissue for histologic determination, bacterial culture or for use in urease detection kits.

Urease detection kits are inexpensive and easy to use. Biopsies from the gastric mucosa are placed in a well containing a yellow colored agar gel which contains urea and a pH indicator. Urease cleaves urea liberating ammonia, which is alkaline turning the agar color red, so indicating the presence of a urea-producing organism. The test enables the determination of the *H. pylori* status of the patient within 24 h, with a substantial proportion giving a positive result within a few hours[8]. This represents a clear advantage over the costly and labor-intensive method of histological examination with special stain.

The aims of our study were to: (1) evaluate the sensitivity and specificity of two commercially available urease detection kits; (2) compare the time interval required for each kit to give a positive result; and (3) determine whether any differences would expedite patient management and save resources, by enabling treatment to be prescribed before patients are discharged from the endoscopy unit, thus avoiding a follow-up appointment.

MATERIALS AND METHODS

The study protocol was approved by the Hospital Ethics Committee. Patients over the age of 18 years referred for upper gastrointestinal endoscopy, in whom *H. pylori* detection was indicated, were enrolled prospectively, after written informed consent was obtained. Before gastroscopy, patients were asked whether they were, or had been in the previous 14 d, on treatment with proton pump inhibitors (PPIs), histamine type 2 receptor antagonists (H_2A), antibiotics, bismuth, or sucralfate. Patients not on PPIs, antibiotics, H_2A, bismuth or sucralfate for up to 14 d prior to the endoscopy, for the purpose of analysis were subsequently assigned to Group 1 and patients who were on, or had been on any of the above medication in the previous 14 d were assigned to Group 2. Patients on anticoagulants or with known prolonged international normalized ratio (INR), activated partial thromboplastin time (aPTT), or platelet count below 100 000/mL were excluded. Gastroscopy was performed routinely under light intravenous sedation and local anesthetic spray to the oropharynx.

The two urease detection kits used for comparison in this study were (1) the *campylobacter*-like organism (CLO) test Rapid Urease Test (Kimberly-Clark, Utah, USA), the gel of which contains urea United States Pharmacopeia (29 mg/mL), phenol red (a pH indicator), buffers and a bacteriostatic agent to prevent the growth of contaminating urease-positive organisms and (2) the *H. pylori* Quick test (Biohit Plc, Helsinki, Finland).

Both kits were kept at room temperature for at least 10 min prior to endoscopy. At endoscopy, two biopsy specimens, one from the antrum and one from the body (mid greater curve) of the stomach[7] were obtained for each urease test, each pair $\leqslant$ 1 cm apart. Each tissue pair was embedded in the same gel-containing well of the kits under investigation. Samples for the two urease tests were taken in a random order (sealed envelope). In each instance, following the biopsies for the urease tests, three biopsies from the antrum and two from the body of the stomach were obtained (within 1 cm of the previous biopsies) for histology/Giemsa and immunohistochemical staining. For each set of biopsies a new disposable spiked forceps with fenestrated cup was used (cup diameter 2.5 mm, Wilson Cook Medical Inc., Winston-Salem, NC, USA). The exact time of the placement of the biopsies in the urease test wells was recorded and the wells inspected for color change at 2 min, 30 min, 2 h and 24 h. The test was assigned positive when there was a color change of at least 2 mm radius of red cloud around the biopsy specimen, or complete color change of the yellow well to red or magenta.

Patients were discharged after 30-45 min post-endoscopy. Where a positive result was obtained, *H. pylori* eradication therapy was prescribed prior to discharge. The number of prescriptions issued before discharge was recorded. Patients not issued a prescription prior to discharge were given follow-up appointments for the result of the urease test and prescription of eradication therapy, where indicated. The financial burden of these extra appointments was calculated from data supplied by the accounts department of our hospital, comprising estimated administrative costs and cost of medical time.

Histology

The gastric mucosa tissue was fixed by a routine fixation system and was embedded in paraffin blocks. A series of three to four thick sections of each block were used for routine stains (hematoxylin/eosin-Giemsa) and immunohistochemistry. Immunohistochemical evaluation was performed as follows: de-paraffined sections of all blocks were pretreated in citrate buffer, pH 6.0 for 10-20 min followed by cooling at room temperature for 20 min. The primary antibody was then added (polyclonal rabbit anti-*H. pylori* serum at 1:250 dilution; Thermo Fischer Scientific, Runcorn, Cheshire, UK) and incubated for 30 min at room temperature. To detect antibody, a visualization system with diaminobenzene was used. Giemsa and immunostained slides were examined independently by two experienced histopathologists (Filippidis T and Leontara V)

Table 1 Sensitivity, specificity and predictive values for *Campylobacter*-like organism test and Quick test (all patients)

Test (at 24 h)	True positive	True negative	Total
CLO test			
Positive	40	1	41
Negative	0	144	144
Quick test			
Positive	39	1	40
Negative	1	144	145

Campylobacter-like organism (CLO) test: sensitivity 100% [95% confidence interval (CI): 91.24-100], specificity 99.3% (95% CI: 96.2-99.88), positive predictive value (PPV) 97.6% (95% CI: 87.4-99.57), negative predictive value (NPV) 100% (95% CI: 97.4-100); Quick test: sensitivity 97.5% (95% CI: 87.12-99.56), specificity 99.3% (95% CI: 96.2-99.88), PPV 97.5% (95% CI: 87.12-99.56), NPV 99.3% (95% CI: 96.2-99.88).

who were blind to the urease test results, using light microscopy; first separately and then their results were compared. Any differences were resolved by discussion between the two histopathologists. A true positive test was determined when any two of the four tests (CLO test, Quick test, Giemsa stain, immunohistochemical stain) were positive.

Statistical analysis

The sensitivity, specificity, positive and negative predictive values of the urease tests were determined for the overall number of the patients and separately for the group of patients not on PPIs, antibiotics, H_2A, bismuth or sucralfate for up to 14 d prior to the endoscopy (Group 1) and for the group of patients who were on, or had been on any of the above medication in the previous 14 d (Group 2).

Statistical comparison of the two urease tests was by the student *t*-test for two dependent proportions, χ^2 test and the McNemar test. A statistically significant difference in the comparison of the two kits was considered when *P* value was $\leqslant 0.05$. Confidence intervals (CI) were determined at the 95% level.

RESULTS

Sensitivity and specificity of CLO test and Quick test at 24 h - all patients

Between April and October 2007, 185 adult patients (101 male, 84 female); age range 18-82, mean 49 years, were entered into the study. One hundred and thirty were outpatients (70%) and 55 (30%) inpatients. The overall results were as follows.

CLO test was positive at 24 h in 41 cases (22%) and negative in 144 cases (78%). Quick test was positive at 24 h in 40 cases (22%) and negative in 145 cases (78%). Histology/Giemsa/immunohistochemistry was positive for *H. pylori* in 44 cases (23.8%).

For all 185 patients, the sensitivity, specificity, positive (PPV) and negative predictive value (NPV) for the CLO test and Quick test were similar (Table 1). The concordance of the CLO test and Quick test for a positive result was 95% and for a negative result was 98%.

Table 2 Sensitivity, specificity and predictive values of the *Campylobacter*-like organism and Quick tests in Group 1

Test (at 24 h)	True positive	True negative	Total
CLO test			
Positive	26	0	26
Negative	0	79	79
Quick test			
Positive	25	0	25
Negative	1	79	80

Campylobacter-like organism (CLO) test: sensitivity 100% [95% confidence interval (CI): 87.13-100], specificity 100% (95% CI: 95.36-100), positive predictive value (PPV) 100% (95% CI: 87.13-100), negative predictive value (NPV) 100% (95% CI: 95.36-100); Quick test: sensitivity 96.1% (95% CI: 81.11-99.32), specificity 100% (95% CI: 95.36-100), PPV 100% (95% CI: 86.68-100), NPV 98.7% (95% CI: 93.25-99.78).

Table 3 Sensitivity, specificity and predictive values of the *Campylobacter*-like organism and Quick tests in Group 2

Test (at 24 h)	True positive	True negative	Total
CLO test			
Positive	14	1	15
Negative	0	65	65
Quick test			
Positive	14	1	15
Negative	0	65	65

Campylobacter-like organism (CLO) test: sensitivity 100% [95% confidence interval (CI): 78.47-100], specificity 98.5% (95% CI: 91.9-99.73), positive predictive value (PPV) 93.3% (95% CI: 70.18-98.81), negative predictive value (NPV) 100% (95% CI: 94.42-100); Quick test: sensitivity 100% (95% CI: 78.47-100), specificity 98.5% (95% CI: 91.9-99.73), PPV 93.3% (95% CI: 70.18-98.81), NPV 100% (95% CI: 94.42-100).

Comparison of CLO and Quick test for patients on or off antisecretory drugs or antibiotics

Of the total 185 patients, Group 1 comprised 105 patients of whom 31 (29%) were inpatients. Group 2 comprised 80 patients of whom 24 (30%) were inpatients. None had been on bismuth or sucralfate. At 24 h, sensitivity, specificity, PPV and NPV was the same for the two kits, both for Group 1 and Group 2 (Tables 2 and 3).

Table 4 displays separately the results of the two urease test kits for Group 1 and 2. At 30 min, taking the CLO test and Quick test together, a total of 33 out of 51 tests were positive in Group 1, as compared to only 12 out of 30 in Group 2 ($P = 0.03$). At 2 h, there was no statistically significant difference between Group 1 and Group 2 ($P = 0.11$). In Group 1, 13 out of 26 CLO tests and 20 out of 25 Quick tests were positive at 30 min ($P = 0.02$), with no difference at 2 h. There was no statistically significant difference in the rapidity of the two urease tests at 30 min and 2 h in Group 2 ($P = 0.13$, $P = 0.14$, respectively).

Comparison of rapidity of a positive result for the CLO and Quick tests

The number of positive CLO and Quick tests for all patients at 2 min, 30 min, 2 h and 24 h is shown in Table 5. Of a total of 40 positive Quick tests at 24 h, only 12 re-

Table 4 Number of patients with a positive *Campylobacter*-like organism and Quick test at 2 min, 30 min, 2 h, 24 h for Groups 1 and 2

Time	Group 1		Group 2	
	CLO test	Quick test	CLO test	Quick test
2 min	2	5	0	3
30 min	13[a]	20[a]	4	8
2 h	23	25	11	14
24 h	26	25	15	15

[a]$P = 0.02$. CLO test: *Campylobacter*-like organism test.

Table 5 Number of patients with a positive *Campylobacter*-like organism and Quick test at 2 min, 30 min, 2 h, 24 h (all patients)

Time	CLO test	Quick test	*P*-value
2 min	2	8	0.03
30 min	17	28	0.05
2 h	34	39	0.28
24 h	41	40	0.45

CLO test: *Campylobacter*-like organism test.

mained negative at 30 min (30%), whereas 24 of a total of 41 positive CLO tests at 24 h (58%) remained negative at 30 min ($P = 0.001$). This enabled the prescription of *H. pylori* eradication therapy before departure from the endoscopy unit for 28/40 patients with a positive Quick test at 30 min and only 12 (30%) follow-up appointments were given.

Estimation of differences in financial costs and resources

Based on the above results if the CLO test had been used alone, only 17 (41.5%) prescriptions would have been possible ($P = 0.05$) prior to discharge and 24 (58%) follow-up appointments would be needed ($P = 0.001$). The additional financial cost of each of the additional 12 follow-up appointments at our hospital, for consultation and the prescription of eradication therapy, would be 17 Euros in administrative costs and 55 Euros in medical time (total: 72 Euros or 96 USD).

At our unit, just over 2000 gastroscopies are performed annually. Given our observed overall prevalence of *H. pylori* colonization of 41/185 (22%), we can expect 440 *H. pylori*-positive cases each year. Extrapolating from the data we present here on a difference of 28% in negative results at 30 min (58% CLO negative at 30 min *vs* 30% Quick negative), if the Quick test was used in preference to the CLO test, a saving of 123 follow-up appointments (total: 8856 Euros or 11 808 USD) would be achieved at our unit each year.

DISCUSSION

The diagnosis of *H. pylori* infection relies on various testing methods, with the gold standard being histology/staining[9]. Urease testing can provide rapid testing in the endoscopy suite, or in the hours following, but does not provide a gold standard assessment of infection.

We selected the CLO test and the Quick test for comparison because they were available locally. We considered that comparison of a greater number of urease test kits would not be justified due to the excessive number of gastric biopsies that this would entail.

Our results indicate, by using two biopsies placed in the same well, that there is no difference in the overall performance of the CLO test and Quick test at 24 h, with sensitivity at 100% and 97.5%, and specificity at 99%, respectively. There was, however, a significant difference in the rapidity of a positive test, in favor of the Quick test, which resulted in a significantly greater number of prescriptions issued prior to discharge at 30-45 min than would have been the case if the CLO test had been used alone.

Previous studies using similar methods also reported the sensitivity of the urease detection kits to be over 90%[10-12]. Goh *et al*[11] compared the HUITAI rapid urease test to histology and culture for *H. pylori* detection. Two biopsy specimens were used (antrum and body of stomach), as in our study. The sensitivity and specificity of the kits were 98.2% and 99%, respectively. In another study by Wong *et al*[12], the PyloriTek kit was evaluated using as gold standard histology and an in-house rapid urease test. In this study, only one biopsy from the antrum was used yielding 96.3% sensitivity and 97.9% specificity, and the benefit of the addition of a corpus biopsy was found to be marginal[12].

The results from the comparison of the reaction time of Groups 1 and 2 (Table 4) indicate that in patients with recent intake of antisecretory drugs or antibiotics the positivity of both urease tests is delayed at 30 min, although the final result at 24 h is not influenced. These findings are in agreement with those of van Keeken *et al*[10]. On the other hand, a decrease in sensitivity, in addition to delayed positivity, was reported by Prince *et al*[13], whilst Midolo *et al*[14] reported that false positive tests when acid suppression therapy is in use occur only after 24 h of incubation. The mechanism by which these medications interfere with the results is thought to be either by directly inhibiting *H. pylori* urease, or by changing the *H. pylori* colonization pattern[13].

There have been a number of previous comparisons of the speed of urease test kits: van Keeken *et al*[10] compared the accuracy and reaction time of a new dry rapid urease test, the GUT test, with the CLO test, culture and histology. The urease test was found reliable to read 60-120 min after endoscopy. Said *et al*[15] compared the accuracy and reaction time of a urease test, the Pronto Dry, with the CLO test and histology. A positive reaction time was achieved at 30 min, similar to the present study. In the study by Goh *et al*[11], the rapidity of the HUITAI rapid urease test was also examined. The median positive reaction time was 1.0 min (25%-75% inter-quartile range: 1.0-3.0 min); more rapid than that observed in the present study[11]. However, no data were given concerning the rapidity of the HUITAI test and its possible impact on resources. Caution should be exercised when

comparing studies of urease test reaction times in different populations, such as the European and Far Eastern. A crucial determinant of the rapidity of a positive urease test is the bacterial load present in the gastric biopsies. This may be higher in the Far East[16].

In our study, there was a significant difference in the rapidity of a positive urease result at 2 and 30 min after placement of the biopsies in the test wells (Table 5), in favor of the Quick test. As a result, we were able to prescribe *H. pylori* eradication therapy before discharge from the endoscopy unit in a significantly higher number of patients (so obviating the need for follow-up visit for the prescription of eradication therapy) than would have been the case if the CLO test had been used alone. The prevalence of *H. pylori* infection of 22% observed in our study is consistent with the 19% reported in a recent seroepidemiological study of Hellenic Navy recruits[17]. This rate is much lower than that reported in studies of the previous decade and is thought to be due to an improvement in lifestyle and socioeconomic status, in line with observations in other developed countries[16-18].

On the basis of our results we calculated that there would be a substantial annual saving in medical and administrative time as well as financial cost, if we adopted the Quick test in preference to the CLO test. In busier endoscopy units or areas of higher *H. pylori* prevalence, the benefit would be higher. Precise financial savings for each endoscopy unit would need to be calculated according to the outpatient follow-up protocol and to local costs. These vary widely between countries and institutions. Where the practice of endoscopy units is to delegate the reading of the urease test and prescription of eradication therapy to other providers, the cost saving would be transferred to the latter.

We conclude that in selecting from locally available urease test kits, direct comparison of the rapidity of a positive result is worthwhile because the appropriate choice of kit would result in a significant saving of resources.

COMMENTS

Background

Helicobacter pylori (*H. pylori*), is a urease (enzyme) producing organism responsible for chronic active gastritis, peptic ulcer disease, gastric cancer and mucosa associated lymphoid tissue lymphoma. One method of rapid detection is by the use of urease detection kits which are inexpensive and easy to use. These kits consist of a well containing a yellow colored agar gel; during gastroscopy, biopsies from the gastric mucosa are placed in the well. The presence of *H. pylori* will turn the agar color red, so indicating the presence of *H. pylori*. The test enables the determination of the *H. pylori* status of the patient within 24 h, and therefore the prescription of eradication therapy.

Research frontiers

According to the literature many urease detection kits have been studied for their sensitivity and specificity as well as for their rapidity. In this article, the authors emphasize the impact of the rapidity of the test on the financial and administrative costs.

Innovations and breakthroughs

The preferential use of a rapid urease test kit results in substantial annual savings in medical and administrative time as well as in financial cost.

Applications

Direct comparison of locally available commercial urease tests is worthwhile because it may lead to saving of resources.

Peer review

The diagnosis of *H. pylori* infection relies on various testing methods, with the gold standard being histology/staining. Urease testing can provide rapid testing in the endoscopy suite, or in the hours following, but does not provide a gold standard assessment of infection.

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