Helicobacter pylori in the critically ill patient
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USEFULNESS OF A FAECAL TEST FOR THE DETECTION OF

Helicobacter pylori antigens in critically ill patients

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Abstract

Introduction: Helicobacter pylori plays a major role in the pathogenesis of gastric and duodenal ulcer disease. It is unknown whether H. pylori plays a role in the formation of stress ulceration in critically ill patients. A simple and reliable test is necessary to study H. pylori infection in critically ill patients at risk for stress ulceration. Previously we have shown that the LARA-13C-urea breath test reliably detects H. pylori infection in these patients. In contrast, the presence of antibodies against H. pylori in serum per se does not indicate H. pylori infection. In this study we compare the detection of H. pylori antigens in a faecal sample with both H. pylori detection using the LARA-13C-urea breath test and with the serological assessment of antibodies against H. pylori.

Study design: Prospective observational cohort analysis.

Methods: Patients admitted to a mixed surgical and medical intensive care unit were studied. Patients were included when mechanical ventilation was instituted. Patients were excluded once they were admitted after elective surgery and once they did not produce stools within 3 days after admission. Informed consent was obtained from the nearest relatives. Immediately after admission a Laser Assisted Ratio Analyser (LARA)-13C-urea breath test was performed and blood was drawn for antibody detection.

Results: In the 3 month study period 129 mechanically ventilated patients were admitted. Ninety-six of them (74%) were excluded because a faecal sample could not be obtained within 3 days. Compared with the LARA-13C-urea breath test, the sensitivity of the faecal antigen test was 75%, the specificity and the positive predictive value were 100% and the negative predictive value was 87.5%. Compared with antibody detection in serum the sensitivity and the negative predictive value of the faecal antigen test were 33.3% and the specificity and the positive predictive value were 88.8%.

Conclusion: The presence of faecal H. pylori antigens is highly suggestive for H. pylori infection. However, the inability to obtain a faecal sample in most patients within 3 days and the low sensitivity because of the recent use of antibiotics, makes this test less suitable to screen critically ill patients for the presence of H. pylori infection.
Introduction

*Helicobacter pylori* plays a major role in the pathogenesis of gastric and duodenal ulcer disease [1]. Whether *H. pylori* plays a role in the formation of stress ulceration in critically ill patients is still unknown. To study the role of *H. pylori* in stress ulcer formation, a diagnostic test is necessary that is easy to use for the screening of critically ill patients. Culture and histopathology are used as the golden standard for the detection of *H. pylori*. However, these tests are not suitable for screening a large study population because they need an invasive procedure and are time consuming. Previously we found that the Laser Assisted Ratio Analyser (LARA)-¹³C-urea breath test is an accurate test for the detection of *H. pylori* in critically ill and mechanically ventilated patients [2]. Serology does not indicate active *H. pylori* infection and false negative results may be caused by haemodilution or blood loss [2]. In a small stool sample *H. pylori* antigens can be detected in case of infection with this micro-organism [3]. The presence of these antigens indicate current *H. pylori* infection. This analysis of faeces is not influenced by possible flaws such as haemodilution and blood loss. Therefore, the faecal test for antigen detection may be useful for screening critically ill patients for the presence of current *H. pylori* infection. In this study we compare a test for the detection of faecal *H. pylori* antigens with serological antibody detection and with the LARA-¹³C-urea breath test.

Methods

Study design
Prospective observational cohort analysis.

Patients
During a 3 months period all patients admitted to the intensive care unit for emergency reasons with an expected stay of at least 24 hours and requiring mechanical ventilation were included in the study. Informed consent was obtained from the nearest relatives. Excluded were patients admitted after uncomplicated elective surgery because of the limited severity of their disease and short length of stay. In addition, patients with gastric perforation and gastric surgery within 24 hours before admission were excluded because of inability to perform a LARA-¹³C-urea breath test in this situation. Patients with pulmonary oedema requiring positive end expiratory pressure (PEEP) ventilation with pressures of 15 cm H₂O or more were excluded for the same reason. In addition, the patients had to produce stools within 72 hours after admission. The local ethical and scientific committees approved the study.
Patients were classified as surgical patients when any surgical intervention was performed within 7 days prior to admission to the intensive care. All other patients were classified as medical patients.

Detection of Helicobacter pylori

*H. pylori* antigens were detected in a 2 ml stool sample by an enzyme immunoassay (EIA) (HpSA™, Meridian Diagnostics, Inc., Cincinnati, OH, USA) which was produced within 72 hours after admission to the intensive care unit. The stool samples were transported to the laboratory immediately after collection and stored at -20°C. All faecal samples were analysed simultaneously at the end of the study period according to the manufacturer's protocol. The Laser Assisted Ratio Analyser (LARA)-¹³C-urea breath test (Alimenterics™ Inc., New Jersey, USA) was used to detect current *H. pylori* infection as previously described [2]. The patients were tested within one hour after the onset of mechanical ventilation. The test was performed by collecting exhaled air at baseline, 30 and 60 minutes after administering 100 mg of ¹³C-urea through the nasogastric tube. The LARA determines the ratio of ¹³CO₂ to ¹²CO₂ in the exhaled air. A ratio of more than 6.1 delta units in either the 30 minutes or the 60 minutes breath sample was considered a positive test result indicating the presence of *H. pylori* [4]. We validated this test previously in mechanically ventilated patients [2].

Blood samples for serological antibody detection were taken immediately after admission to the intensive care unit. Serum IgG antibodies against *H. pylori* were quantitatively determined by enzyme linked immunosorbent assay (HM-CAP™ ELISA Enteric Products, Inc. Stony Brook, NY). A cut off level of 1.8 U/l was used [5].

Statistical analysis

Sensitivity, specificity, negative and positive predicting values and likelihood ratio of the detection of *H. pylori* by the faecal antigen test were calculated as compared with *H. pylori* infection detected by either the LARA-¹³C-urea breath test or serological antibody titre.

Results

During the 3 month study period 129 patients fitted the inclusion criteria on admission to the intensive care. However, 96 patients (74%) did not produce stools within three days after admission. Therefore, only 33 patients were included (26%). The mean age of the included patients was 65.8 years (SD 14.6, range 23 – 85 years). Nine patients were female, 24 were male. Fourteen patients were classified as surgical and 19 as medical patients.
The mean Acute Physiology and Chronic Health Evaluation score (APACHE II) was 25.2 (SD 8.3 and range 12 – 51) with a median predicted mortality of 0.39 (SD 0.27 and range 0.072 - 0.987). The mean Simplified Acute Physiology Score (SAPS II) was 52.8 (SD 18.4 and a range 22 – 93) with a median predicted mortality of 0.44 (SD 0.29 and a range 0.05 – 0.97). Observed intensive care mortality was 39.4% and observed hospital mortality was 51.5%.

Table 1
2x2 table of faecal *H. pylori* antigen test (HpSA) and LARA-\(^{13}\)C-urea breath test

<table>
<thead>
<tr>
<th>N=33</th>
<th>LARA-UBT positive</th>
<th>LARA-UBT negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal antigen test positive</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Faecal antigen test negative</td>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 2
2x2 table of faecal *H. pylori* antigen tests (HpSA) and serology

<table>
<thead>
<tr>
<th>N=33</th>
<th>Serology positive</th>
<th>Serology negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal antigen test positive</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Faecal antigen test negative</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>
Table 3

_Helicobacter pylori_ detection rates of faecal _H. pylori_ antigen test (HpSA) compared to the LARA-¹³C-urea breath test and serology. Hp+: _H. pylori_ infection present; Hp-: _H. pylori_ infection absent; Sens.: Sensitivity; Spec.: Specificity; PPV: Positive predicting value; NPV: Negative predicting value; LR(+): Likelihood ratio of a positive test; LR(-): Likelihood ratio of a negative test; UD: Undefined.

<table>
<thead>
<tr>
<th>method of detection:</th>
<th>No. Hp+</th>
<th>No. Hp-</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR(+)</th>
<th>LR(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HpSA vs. LARA</td>
<td>12</td>
<td>21</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>87.5</td>
<td>UD</td>
<td>4</td>
</tr>
<tr>
<td>HpSA vs. serology</td>
<td>24</td>
<td>9</td>
<td>33.3</td>
<td>88.8</td>
<td>88.8</td>
<td>33.3</td>
<td>3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

_H. pylori_ infection as determined by a positive LARA-¹³C-urea breath test was found in 12 of the 33 patients (36%). Antibodies against _H. pylori_ were present in 24 out of 33 patients (73%). The median antibody titre was 3.04 U/l with a SD of 2.22 U/l (range 0.26 - 8.4 U/l). The result of the faecal _H. pylori_ antigen tests (HpSA) of 33 patients is compared to the LARA-¹³C-urea breath test and serological antibody detection which is shown in table 1 and table 2. The agreement of HpSA with the LARA-¹³C-urea breath test was 91%, the agreement with the serological antibody detection was 48%. Sensitivity, specificity, positive predictive value and negative predictive value of the faecal antigen test compared to the LARA-¹³C-urea breath test and serological antibody detection are summarised in table 3.

**Discussion**

Theoretically, the faecal test for the detection of _H. pylori_ antigens is a non-invasive and easy method to detect _H. pylori_ infection in critically ill patients. In addition the stool samples may be stored before analysis and the results are not biased by possible flaws that disturb other tests for the detection of _H. pylori_. However, the results of this study show that the faecal test for the detection of _H. pylori_ antigens has major disadvantages in critically ill patients. Seventy-four percent of the 129 admitted patients in the study period could not be included because they did not produce stools within three days after admission. Stools that are produced later may be less suitable for testing because of (antibiotic) medication given to the patients. However, the present study was not designed to test that hypothesis. A preliminary study showed that the optical density (OD) of the HpSA decreased rapidly during treatment for _H. pylori_ [6]. After 5 days the mean OD reached...
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...the cut-off value but occasionally that threshold was reached sooner. Therefore, the sensitivity of the HpSA decreases rapidly after the institution of H. pylori suppressive antibiotics. In the present study the patients were all treated with at least two antibiotics which suppresses H. pylori (cefotaxime and tobramycin) as part of selective decontamination of the digestive tract. The present study shows that when a stool sample is collected and tested positive for the H. pylori antigens, the patient is very likely to have a current H. pylori infection. This is indicated by a positive predicted value of 100%. Also, a patient without H. pylori infection will have negative test results by the HpSA as indicated by the specificity of 100%. However, 25% of the patients with H. pylori infection as determined by a positive LARA-^{13}C-urea breath test, were tested negative with the HpSA. Therefore we conclude that a positive HpSA result strongly suggests active H. pylori infection but a negative test result does not rule out H. pylori infection. The results of the LARA-^{13}C-urea breath test and the faecal antigen test were in agreement in 91% of the patients. In a European multicenter study the sensitivity of the HpSA was found to be 90% compared to histopathology and 94% compared to LARA-^{13}C-urea breath test [3]. The 75% sensitivity compared to the LARA-^{13}C-urea breath test that we found in the present study may be explained by the recent use of antibiotics in some of our patients.

The results of the HpSA and antibody detection in serum were in agreement in only 48% of the patients. The sensitivity and specificity of the HpSA compared to serological antibody detection were 89%. The relatively low sensitivity and specificity of the faecal test compared to the antibody detection in serum may in part be due to the fact that antibodies can be detected for a prolonged period of time after eradication of the infection. Therefore the detection of antibodies does not necessarily mean current H. pylori infection. H. pylori antigens in a stool sample, however, can only be detected in case of current H. pylori infection.

Previously we have shown that the presence of antibodies against H. pylori in serum was not well correlated with a positive result of the LARA-^{13}C-urea breath test [2]. The present study confirms these results of serological antibody detection in critically ill patients. Paré was the first to hypothesise about the role of H. pylori in the pathogenesis of stress ulceration in critically ill patients [7]. Only a limited number of studies have explored this hypothesis [8-11]. Most of these studies are preliminary reports and used the presence of antibodies in serum for the detection of H. pylori infection. Previously we have shown that the presence of antibodies against H. pylori in serum was not related to gastric or duodenal mucosal injury [12]. In contrast, H. pylori infection determined by the LARA-^{13}C-urea breath test was significantly related to the presence of major mucosal injury in critically ill and mechanically
ventilated patients [12]. Reliable detection of H. pylori is necessary to study the role of this micro-organism in the pathogenesis of stress ulceration in mechanically ventilated critically ill patients. The present study shows that the detection of faecal H. pylori antigens is highly suggestive for H. pylori infection. However, in a majority of critically ill patients a stool sample could not be obtained within 3 days which is the main limitation of the faecal H. pylori antigen test in these patients. It may be possible to improve the availability of stool samples by active collection of faeces from the rectum. However, in this study we did not do that. In addition a relatively low sensitivity of the faecal antigen test is found compared to the LARA-^{13}C-urea breath test which may be due to the recent use of antibiotics. These two results made the faecal antigen test less suitable to screen our population of critically ill patients for the presence of H. pylori infection.
References