Helicobacter pylori in the critically ill patient
van der Voort, P.H.J.

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Chapter 6

HELICOBACTER PYLORI INFECTION BUT NOT SEVERITY OF DISEASE DETERMINES GASTRIC PERMEABILITY IN CRITICALLY ILL PATIENTS

P.H.J. van der Voort¹,², D.F. Zandstra¹, R.W.M. van der Hulst³,⁴, A. van der Ende⁵, A.A.M. Geraedts⁶, F. Hoek⁷ and G.N.J. Tytgat³

¹ Dept. of intensive care, Onze Lieve Vrouwe Gasthuis, Amsterdam
² Dept. of intensive care, Medisch Centrum Leeuwarden-Zuid, Leeuwarden
³ Dept. of gastroenterology, Academic Medical Center, Amsterdam
⁴ Dept. of internal medicine and gastroenterology, Kennemer Gasthuis, Haarlem
⁵ Dept. of medical microbiology, Academic Medical Center, Amsterdam
⁶ Dept. of gastroenterology, Onze Lieve Vrouwe Gasthuis, Amsterdam
⁷ Dept. of clinical chemistry, Academic Medical Center, Amsterdam
3. Van der Huijst B.W.M., Van der Huijst P.H.J., Aron D.R., Deraedt M.
4. Determining the severity of Helicobacter pylori infection in critically ill patients.
Abstract

Introduction: Intestinal permeability is increased in patients with severe disease such as burns, sepsis and trauma. Dual sugar tests are used to measure intestinal permeability. Gastric permeability can be studied with the sucrose loading test. However, this test has not been performed previously in critically ill patients. An increase in gastric permeability may theoretically predispose for stress ulcer formation. Helicobacter pylori is associated with gastric and duodenal ulcer disease and may be a risk factor for stress ulcer formation. Healthy volunteers infected with H. pylori show an increase in sucrose permeability of the stomach. In the present study the relation between gastric permeability measured by the sucrose loading test and both H. pylori infection and severity of disease scores (APACHE II, SAPS II, MPM 0 and MPM 24) are studied in critically ill patients.

Methods: Consecutive mechanically ventilated patients admitted to the intensive care with an expected stay of at least 24 hours were included in the study. H. pylori was detected by the Laser Assisted Ratio Analyser-13C-urea breath test. The severity of disease was determined by APACHE II, SAPS, MPM 0 and MPM 24 scores. Gastric permeability testing was performed by instillation of 100 gr. of sucrose in 250 ml of water via the nasogastric tube. Sucrose excretion was determined in the urine that was collected during the next 5 hours.

Results: 153 patients were included. Median sucrose excretion was 442 mg (mean 985 mg, SD 2420 mg, range 1.0 – 27851 mg). In 63 patients with H. pylori infection the median sucrose excretion was 641 mg (mean 996 mg, SD 1168 mg, range 10 – 1169 mg) compared to 329 mg (mean 976 mg, SD 3009 mg, range 1.0 – 27851 mg) in 90 patients without H. pylori infection (p=0.007). A correlation between any of the severity of disease scores and sucrose excretion in the urine was not found. The same results were found after correction for renal function.

Conclusion: Gastric permeability measured by the sucrose loading test was increased by H. pylori infection but not by severity of disease measured by APACHE II, SAPS, MPM 0 or MPM 24. H. pylori infection leads to a significantly impaired integrity of the gastric mucosa, thereby possibly facilitating stress ulcer formation.

Introduction

Intestinal permeability testing has been used for the detection of gut mucosal injury in critically ill patients [1]. Intestinal permeability can be studied by dual sugar tests. Usually excretion of lactulose/mannitol or cellobiose/rham-
Helicobacter pylori in the critically ill patient.

Nose ratio's in the urine after oral ingestion of these sugars are determined. Increased permeability has been shown in many patient groups with severe disease [2-5]. Also, the severity of disease measured by APACHE II scores in some studies correlates with intestinal mucosal permeability [6]. Permeability tests are supposed to measure the degree of mucosal injury of the small bowel. However, the most frequent mucosal lesion in critically ill patients is stress ulceration in the stomach and duodenal bulb. None of the aforementioned dual sugar tests is specific for gastric mucosal permeability. In contrast, the sucrose loading test has been developed to measure gastric permeability after mucosal injury [7]. Sucrase degrades sucrose to fructose and glucose in the duodenum and jejunum. Therefore increased intestinal permeability distal from the stomach does not affect the sucrose excretion in the urine. The sucrose loading test can detect gastric ulceration with a sensitivity of 84% and a specificity of 96% [8]. Gastric permeability for sucrose is also increased by Helicobacter pylori infection and the eradication of H. pylori decreases sucrose recovery from the urine [9].

In contrast to dual sugar tests for the detection of intestinal permeability which have been used extensively in critically ill patients, sucrose loading tests have not been used in this population before. The high prevalence of endoscopically detected gastric lesions (66 – 82% [10,11]) indicate that gastric mucosal injury and increased gastric permeability is widely present in unselected critically ill patients. In the present study we tested the hypothesis that gastric mucosal permeability in critically ill patients, determined by the sucrose loading test, is related to the severity of disease, measured by APACHE II and other scores, and to H. pylori infection.

**Methods**

**Patients**

Consecutive 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. Exclusion criteria were admission after uncomplicated elective surgery, gastric perforation and gastric surgery within 24 hours before admission because of inability to perform an urea breath test in this situation. Patients with pulmonary oedema requiring positive end expiratory pressure (PEEP) ventilation with a pressure of 15 cm H₂O or more were excluded for the same reason. Scoring systems for determination of the severity of disease (APACHE II, SAPS, MPM 0 and MPM 24) were calculated in the first 24 hours after admission. A patient was categorised as a surgical patient when an operation was performed within 7 days prior to admis-
sion to the intensive care. A patient was categorised as ‘cardiac surgery’ when the cardiac surgery was performed within 7 days prior to admission. All other patients were categorised as medical patients. The local ethical and scientific committees approved the study.

Detection of H. pylori
The Laser Assisted Ratio Analyser (LARA)-\(^{13}\)C-urea breath test (Alimenterics Inc. New Jersey, USA) was used to detect current H. pylori infection as previously described [12]. The test is performed by collecting exhaled air at base line, 30 and 60 minutes after administering 100 mg of \(^{13}\)C-urea through the nasogastric tube. The LARA determines the ratio of \(^{13}\)CO\(_2\) to \(^{12}\)CO\(_2\) 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 infection. We validated this test previously in mechanically ventilated patients [13]. The test was performed immediately after admission.

Sucrose loading test
The sucrose loading test was performed after the LARA-\(^{13}\)C-urea breath test was completed. The stomach was emptied by suctioning the naso-gastric tube. A sterile solution of 100 g of sucrose in 250 ml of water was instilled via a naso-gastric tube in 15 minutes. All urine was collected during the next 5 hours. The volume of the urine was measured and a representative urine sample was taken and stored at –20°C until use. The amount of sucrose excreted in the urine was measured enzymatically using the sucrose/D-glucose/D-fructose testkit (Boehringer Mannheim, no. 716260) from Roche Diagnostics, Almere, The Netherlands. The analyses were performed on a Cobas Bio analyser (Roche, Almere, The Netherlands). According to this method sucrose was hydrolysed using \(\beta\)-fructosidase at pH 4.6, giving glucose and fructose in equal amounts. After completion of the hydrolysis, glucose and fructose were measured consecutively at pH 7.6, using hexokinase and glucose-6-phosphate. The formation of NADPH was monitored at 340 nm. After consumption of the glucose, fructose was measured by addition of phosphoglucoisomerase for conversion of fructose-6-phosphate to glucose-6-phosphate. The results obtained were corrected for free glucose and fructose present in the urine samples. Sometimes high glucose concentrations were present in the samples, which could influence the result obtained. Samples were then remeasured after dilution. The fructose measurement in the samples were not influenced by high fructose concentrations. Different concentrations of sucrose in water were always referred to as standard in the procedure.
Severity of disease
The severity of the disease for which the patient was admitted to the intensive care unit was determined by the Acute Physiology And Chronic Health Evaluation II (APACHE II) score [14] and the Simplified Acute Physiology System (SAPS II) score [15] 24 hours after admission and the Mortality Prediction Model (MPM) score on admission (MPM 0) and after a period of 24 hours (MPM 24) [16].

Statistical Analysis
Comparison of means was performed using the T-test in case of normal distribution. In case of skewed distribution a logarithmic transformation was performed to reach a normal distribution. A comparison of categorical data between groups was performed by the Chi Square test. Correlation was determined by Spearman's rank correlation. The statistical analysis was made with the SPSS statistical analyser release 8.0.0 (SPSS inc., USA, 1997). A p value < 0.05 was considered to be statistically significant.

Results
Demographic data of 153 included patients are summarised in table 1. The median sucrose excretion was 442 mg (SD 2420 mg, mean 985 mg, range 1.0 – 27851 mg). The median sucrose excretion was 641 mg (mean 996 mg, SD 1168 mg, range 10 – 1169 mg) in 63 patients with *H. pylori* infection compared to 329 mg (mean 976 mg, SD 3009 mg, range 1.0 – 27851 mg) in 90 patients without *H. pylori* infection. The skewed distribution of the sucrose recovery data was changed into a normal distribution by logarithmic transformation. The T-test of these logarithmic data showed a significant higher sucrose recovery in the patients infected with *H. pylori* compared to the patients without *H. pylori* infection (figure 1, p=0.007).

The sucrose excretion was not significantly correlated with either the APACHE II score (figure 2) or SAPS, MPM 0 and MPM 24 score. Adjustment for renal function was performed by multiplying the amount of excreted sucrose by 100 and dividing this by the creatinine clearance (CC) in ml/min: Sucr<sub>adj</sub> = Sucr x 100/CC. Sucr<sub>adj</sub> was related to *H. pylori* infection (p=0.024) but was not related to APACHE II (p=0.54) or the other disease scores.
### Table 1.
Demography and severity of disease scores for the included patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients: N=153 (SD)</th>
<th>Hp positive: N=63 (SD)</th>
<th>Hp negative: N=90 (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>66.7 (14.5)</td>
<td>69.1 (12.3)</td>
<td>65 (15.8)</td>
</tr>
<tr>
<td><strong>Male / Female (N)</strong></td>
<td>92 / 61</td>
<td>40 / 23</td>
<td>52 / 38</td>
</tr>
<tr>
<td><strong>Cardiac surgery (%)</strong></td>
<td>38</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td><strong>General surgery (%)</strong></td>
<td>19</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td><strong>Medical (%)</strong></td>
<td>96</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td><strong>Mean APACHE II (SD)</strong></td>
<td>23.1 (8.2)</td>
<td>24.0 (7.8)</td>
<td>22.5 (8.5)</td>
</tr>
<tr>
<td><strong>Mean APACHE II predicted mortality (SD)</strong></td>
<td>0.42 (0.27)</td>
<td>0.45 (0.27)</td>
<td>0.39 (0.28)</td>
</tr>
<tr>
<td><strong>Mean SAPS II (SD)</strong></td>
<td>49.7 (16.8)</td>
<td>51.7 (16.7)</td>
<td>48.3 (16.8)</td>
</tr>
<tr>
<td><strong>Mean SAPS II predicted mortality (SD)</strong></td>
<td>0.45 (0.28)</td>
<td>0.48 (0.28)</td>
<td>0.43 (0.28)</td>
</tr>
<tr>
<td><strong>Mean MPM 0 (SD)</strong></td>
<td>0.40 (0.27)</td>
<td>0.47 (0.27)*</td>
<td>0.36 (0.26)*</td>
</tr>
<tr>
<td><strong>Mean MPM 24 (SD)</strong></td>
<td>0.46 (0.22)</td>
<td>0.49 (0.23)</td>
<td>0.44 (0.22)</td>
</tr>
</tbody>
</table>

Hp: *Helicobacter pylori*; SD: standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; MPM: Mortality Prediction Model. * p=0.01. All other variables were not significantly different.

Sucrose excretion (mg) 10000 1000 100 10 0  

**Figure 1.**
Sucrose excretion in the urine (mean with 95% CI) in patients with and without *H. pylori* infection.
Discussion

We studied the relation between sucrose permeability of the stomach and both *H. pylori* infection and severity of disease. We found a significant relation between *H. pylori* infection and gastric mucosal permeability in critically ill patients with or without adjustment for renal function. This finding is consistent with a previous study in which *H. pylori* infection was associated with increased sucrose permeability in healthy volunteers [9]. Moreover, increased gastric permeability for sucrose is related to gastric mucosal injury [7].

It is shown now that also in critically ill patients *H. pylori* infection leads to a decreased barrier function of the gastric mucosa. The structure of the mucus in the stomach is affected by *H. pylori* [17]. The mucosal injury and decreased barrier function caused by *H. pylori* infection may therefore lead to back diffusion of acid which is supposed to be an important step in the pathogenesis of stress ulceration [18]. Previously, we have shown that *H. pylori* infection was associated with endoscopically detected mucosal lesions in critically ill patients [10]. The finding of increased gastric permeability to sucrose in case of *H. pylori* infection underlines the role of *H. pylori* in the pathogenesis of stress ulceration. However, ischaemia remains an important determinant of mucosal injury. In the present study we did not measure gastric mucosal ischaemia. Moreover, gastric mucosal ischaemia
can not be monitored routinely in critically ill patients. Tonometry measures gastric mucosal acidosis which is related to hypoxia [19]. Tonometry and APACHE II scores are related in some studies [20] and APACHE II score may also be related to intestinal permeability [6]. In our study APACHE II and other severity of disease scores were not related to gastric mucosal permeability. Neither did we find a significant difference in APACHE II or other scores between the patients with and those without *H. pylori* infection. In a previous study we did not find a correlation between severity of disease scores and endoscopically detected mucosal injury [10]. Therefore, severity of disease measured by APACHE II or other scores did not correlate with either endoscopically detected gastric mucosal injury or gastric sucrose permeability. Theoretically, sucrose excretion may be determined by renal function. We made an adjustment for renal function because some patients were oliguric and had an impaired renal function. However, the relation between the adjusted sucrose excretion and *H. pylori* infection remained significant. In previous studies gastric permeability for sucrose was increased by NSAID induced mucosal injury [7,8]. In the present study NSAID use was limited to the use of low dose aspirin (38 to 100 mg per day) and was equally distributed between patients with and those without *H. pylori* infection.

In conclusion, severity of intensive care disease as determined by APACHE II and other scores was not related to increased gastric mucosal permeability. The presence of *H. pylori* infection was the exclusive determinator for a significantly impaired gastric mucosal integrity. These results indicate that apparent *H. pylori* infection may be one of the key factors in the development of stress ulcer formation.
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References

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