Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Chapter 4

Equally high efficacy of a four, seven and ten days triple therapy to eradicate *Helicobacter pylori* infection in patients with ulcer disease

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Background
In patients with ulcer disease the optimal dose and duration of *H. pylori* treatment containing omeprazole (O), metronidazole (M) and clarithromycin (C) still has to be established. The efficacy might be influenced by M- and C-resistance (R). The aim is to study the effect of duration of OMC-treatment on its efficacy and influence of M-R and C-R on the optimal duration.

Methods
Ulcer patients (n=76) were double-blindly randomized for three treatments of 10 days: OMC4 consisted of 4 days bd 20mg O, 400mg M and 250mg C switched over to 6 days bd 20mg O and placebo (P) (n = 27); OMC7, 7 days bd O20M400C250 and 3 days bd O20P (n = 25); OMC10, 10 days bd O20M400C250 (n = 24). *H. pylori* was assessed by biopsies for culture and histology pre- and 4-6 weeks after OMC therapy. M-R and C-R were assessed by the E-test.

Results
ITT-eradication rates were OMC4 96%, OMC7 92% and OMC10 96% (ns). All the three PP-eradication rates were 100% (95% CI: 85.2-100). Of 75 isolates 16 were MR and 1 was CR.

Conclusion
In *H. pylori* positive ulcer patients OMC4 is highly efficacious and as effective as OMC7 and OMC10. No influence of M-R or C-R was observed.
Introduction

Eradication of *Helicobacter pylori* is recommended for patients with peptic ulcer disease. It will cure the ulcer diathesis without the risk of recurrence or reinfection. Successful eradication of *H. pylori* was difficult to achieve. Mono and dual therapies (a proton pump inhibitor combined with an antibiotic) are almost not or only moderately effective. Nowadays, the recommended eradication therapies, which are most efficacious, consist of a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole, twice daily for at least seven days. The efficacy of regimens is jeopardized by poor patients' compliance. In addition, infection with metronidazole or clarithromycin resistant *H. pylori* organisms may affect the efficacy of eradication therapies. A simple and highly effective *H. pylori* eradication regimen without serious side effects is obligatory to assure a high patient compliance.

Here, the efficacy of anti-*H. pylori* therapy was studied in relation to the duration of therapy and the pretreatment susceptibility to clarithromycin or metronidazole of *H. pylori*. Patients with actual or previous ulcer disease from primary care were treated with a 4, 7 or 10 days regimen, consisting of omeprazole 20 mg, metronidazole 400 mg and clarithromycin 250 mg all twice daily.

Materials and Methods

*Patient population*

This study, which forms a part of a larger study ‘Chronic dyspepsia in General Practice’, was conducted in the period of april 1997- october 1999. Eligible for the study were chronic dyspeptic patients on acid suppressant maintenance therapy in the age of 18-85 years. Chronic dyspepsia was defined as chronic upper abdominal pain/discomfort requiring maintenance acid suppressant drugs in at least the preceding 8 weeks before entry of the study. Patients were identified by means of computerised medication data of all pharmacists co-operating with the participating general practitioners. In the Netherlands all patients are listed and documents are kept in the office of the general practitioner. The original documents were checked by the principal investigator.

The following patients were excluded: patients with documented gastroesophageal reflux disease grade II, III, IV (Savary-Miller); patients with documented significant cardiovascular, pulmonary, renal, hepatobiliary or pancreatic disease or malignancy; patients with sinister dyspeptic symptoms; patients with documented abdominal surgery with relevance to the study; pregnant or lactating women; patients requiring an interpreter; patients taking antibiotics or bismuth containing compounds during the previous month, patients taking NSAID other than carbamazepine; patients with any condition associated with poor compliance
Data about the documented history results of upper GI-endoscopy or barium meal, medication and co-medication of the eligible patient, were obtained by the principal GP-investigator (G.H.) on behalf of the participating GP’s in their practice. Verification and completion of the obtained data took place in a face to face evaluation between the principal GP-investigator and the GP.

All eligible patients were invited to participate by letter from their GP, in which the study was explained. The patients were asked to stop ingestion of their acid suppressant medication at least one week before the day of the upper GI-endoscopy.

Demographic and dyspepsia questionnaires were filled out in hospital. Autochthonic patients were defined as patients born in the Netherlands and allochthonic patients born outside this country (all in non-western countries).

The study was approved by the Institutional Ethics Committee of the Academic Medical Centre and a written informed consent was obtained from the patient at the time of endoscopy.

**Endoscopy and assessment of H. pylori infection**

During each endoscopic procedure, 3 antral and 3 corpus mucosal biopsy specimens were obtained for histological and bacteriological assessment. The biopsy specimens for histological examinations were fixed in 10% buffered formalin and routinely processed. Paraffin sections (5 μm) were cut and stained with hematoxylin and eosin. Biopsy specimens used for bacterial culture were placed in 2 ml of normal saline at 4°C and then rubbed on the surface of horse blood agar plates (7% defibrinated horse blood in Columbia agar base, Oxoid CM 331, Unipath, Basingstoke, England) and horse blood agar plates containing Skirrow supplement (Unipath) as described before. Isolates were identified as *H. pylori* by Gram stain morphology and by urease, oxidase and catalase positivity. Patients were defined as positive for *H. pylori* (the gold standard) if one of the biopsy specimen was positive in culture or in histopathology. *H. pylori* infection was absent if bacterial culture and histopathology readings were all negative. The histopathologist and microbiologist were blinded to each other’s results.

**Metronidazole and clarithromycin susceptibility testing**

The susceptibility to clarithromycin and metronidazole of *H. pylori* was assessed by the E-test (AB Biodisk, Sweden) as described before.

**Randomisation and treatment regimens**

Two weeks after endoscopy patients with an active or inactive (but documented history of) gastric or duodenal ulcer were at random double-blindly allocated to one of the three different treatment regimens:
equally high efficacy of a four, seven and ten days triple therapy

The OMC4-treatment consisted of 4 days twice daily metronidazole 400 mg (M), clarithromycin 250 mg (C) and omeprazole 20 mg (O) and switched over to subsequently 6 days of placebo antibiotics (P) and omeprazole 20 mg (O) twice daily.
The OMC7-treatment consisted of 7 days twice daily metronidazole 400 mg, clarithromycin 250 mg and omeprazole 20 mg and switched over to subsequently 3 days of placebo antibiotics and omeprazole 20 mg twice daily.
The OMC10-treatment consisted of 10 days twice daily metronidazole 400 mg, clarithromycin 250 mg and omeprazole 20 mg.

The principal GP-investigator, discussed the results of the gastroscopy and further treatment with the patient. Information was given about the previous and current concepts of ulcer disease, possible (rarely observed) side effects of therapy and the expectation of a possible final cure of a patient’s ulcer disease and possible complaints after completion of the therapy. A written hand-out about these aspects was also given to the patient. Medication was packed separately for each day and the usage was explained to the patient.
Compliance was assessed by tablet counting and patients were asked to report serious adverse events to the investigator.

Post H. pylori eradication therapy follow up
Patients had a control endoscopy at least 4 weeks after cessation of the regimen and biopsy specimens were again taken for culture and histology according to the aforementioned procedure. Patients, who refused endoscopy, were assessed for \textit{H. pylori} infection by \textsuperscript{13}C Urea Breath Test using a Laser-Assisted-Ratio-Analyser (Alimenterics B.V., Hoofddorp, Netherlands) according to the instructions provided by the manufacturers.\textsuperscript{7,8} The LARA \textsuperscript{13}C Urea Breath Test is an accurate tool for the detection of \textit{H. pylori} with a sensitivity of 93\% and specificity of 96.\textsuperscript{8}

\textbf{Statistics}

Ninety-five per cent confidence intervals for proportions were calculated by the statistical program CIA (confidence interval analysis).\textsuperscript{9}

\textbf{Results}

In fifty four general practices 2230 patients were using longterm acid suppressant medication and 49.6 \% (1083/2230) were using this medication for chronic upper abdominal pain/discomfort, without having one of the exclusion criteria. After invitation to participate in the study 434/1083 (40.1\%) underwent upper gastro endoscopy. After exclusion of two patients (language problem and refusal to further participation) 76 patients with \textit{H. pylori} positive ulcer disease were included.
They were randomised to receive either OMC4 (n=27), OMC7 (n=25) or OMC10 (n=24). Demographic and clinical characteristics are summarized in table 1.

Table 1. Demographic and clinical characteristics of patients with peptic ulcer disease stratified for OMC4 (4 days course-), OMC7 (7 days course-), OMC10 (10 days course of twice daily omeprazole 20 mg/metronidazole 400 mg/clarithromycin 250 mg).

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>OMC4 n=27</th>
<th>OMC7 n=25</th>
<th>OMC10 n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>median age (yr. (range))</td>
<td>54(21-81)</td>
<td>56(31-79)</td>
<td>51(21-81)</td>
<td>52(28-77)</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>53/23</td>
<td>21/6</td>
<td>18/7</td>
<td>14/10</td>
</tr>
<tr>
<td>autochthons / allochthons</td>
<td>49/27</td>
<td>18/9</td>
<td>16/9</td>
<td>15/9</td>
</tr>
<tr>
<td>active ulcer disease</td>
<td>29</td>
<td>12</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>metronidazole resistance</td>
<td>16/75</td>
<td>6/26</td>
<td>1/25</td>
<td>9/24</td>
</tr>
<tr>
<td>clarithromycin resistance</td>
<td>1/75</td>
<td>1/26</td>
<td>0/25</td>
<td>0/24</td>
</tr>
</tbody>
</table>

All patients complied with their dose regimen. No serious side effects were reported. Two patients complained of stomatitis and glossitis but could continue the therapy.

Of the *H. pylori* isolates of 75 patients, 16 (21%) and 1(1%) were resistant to metronidazole and clarithromycin, respectively. The isolate of one patient was not assessed for susceptibility to metronidazole and clarithromycin. Patients younger than 46 year of age were significantly more often colonized with metronidazole resistant *H. pylori* than older patients; 38% (8/21) and 15% (8/54), respectively (p<0.05). The prevalence of metronidazole resistant *H. pylori* infection was not different between autochthonic (8/49) and allochthonic (8/27) patients or between the young (< 45 years of age) autochthonic (2/5) and allochthonic patients (6/16).

Sixty five patients underwent follow-up endoscopy and seven patients $^{13}$C Urea Breath Test (table 2). Four patients refused follow up, either by endoscopy or by $^{13}$C Urea Breath Test. Of these four patients two were colonised with a metronidazole resistant *H. pylori*.

The intention to treat eradication rates were almost equal for the three regimens: OMC4 96% (26/27; CI 95%:81.0-99.9), OMC7 92% (23/25; CI 95%:74.0-99.9) and OMC10 96% (23/24; CI 95%:79.0-99.9) (ns). The per protocol eradication rates were 100% in all three treatment groups with in OMC4 95% CI: 86.8-100, in OMC7 95% CI:85.2-100, in OMC10 95% CI:85.2-100.

No influence on the efficacy of the regimens in relation to duration was observed for metronidazole neither for clarithromycin resistant *H. pylori*.
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Table 2. Treatment results of patients with peptic ulcer disease stratified for OMC4 (4 days course-), OMC7 (7 days course-), OMC10 (10 days course of twice daily omeprazole 20 mg/metronidazole 400 mg/clarithromycin 250 mg).

<table>
<thead>
<tr>
<th>Compliance</th>
<th>All Patients n=76</th>
<th>OMC4 n=27</th>
<th>OMC7 n=25</th>
<th>OMC10 n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>No follow-up result</td>
<td>76/76</td>
<td>27/27</td>
<td>25/25</td>
<td>24/24</td>
</tr>
<tr>
<td>follow-up endoscopy</td>
<td>65</td>
<td>24</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>follow-up ^13^C-UBT</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Discussion
The often advised therapy of first choice for the eradication of *H. pylori* is a 7 days course of PPI, clarithromycin 500 mg and metronidazole 500 mg / amoxicillin 1000 mg. An optimal treatment still has to be established with respect to dose and duration of treatment. The dosages we have used for the antimicrobial part of therapies were clarithromycin 250 mg and metronidazole 400 mg. Very few studies have attempted to measure the minimum duration of a PPI-triple therapy with clarithromycin and metronidazole in patients with ulcer diathesis. Since the influence of susceptibility of *H. pylori* to clarithromycin or metronidazole on the efficacy of the triple therapy in relation to duration is not known, we conducted this study with four, seven and ten days duration regimens.
In intention to treat (ITT) analyses the three regimens used revealed a high *H. pylori* eradication rate ≥90%. After per protocol (PP) analysis a 100% eradication rate was achieved with all regimens, a result independent the duration of the therapy.
This result is more or less comparable with the ITT eradication rate of 91.7% in a five days treatment with twice daily omeprazole 20 mg, metronidazole 500 mg, clarithromycin 500 mg and with the ITT eradication rates of 85-90% with low dosages one-week treatments (twice daily omeprazole 20 mg, metronidazole 400 mg / 500 mg, clarithromycin 250 mg) in ulcer patients.9-15 Previously, an ITT eradication rate of 93.3 % was reported with short-term low dose triple therapy consisting of lansoprazole 30 mg (twice a day for 7 days),
zythromycin 500 mg (once a day for 3 days) and metronidazole 250 mg (twice a day for the same 3 days).\textsuperscript{16}

Although the number of patients in the three different treatment regimens might have been too small to reveal a statistically significant difference between the three regimens, the data obtained in our study could indicate that a 4 days duration is sufficient.

Resistance by \textit{H. pylori} to metronidazole or to clarithromycin and poor compliance are often mentioned as the two main factors responsible for impaired success rates of \textit{H. pylori} eradication therapies.

The prevalence of clarithromycin resistant \textit{H. pylori} and metronidazole resistant \textit{H. pylori} was, 1\% and 21\% respectively. These values are lower than 3.6\% and 35.4\%, respectively, previously reported for the same region of the Netherlands.\textsuperscript{17} The study inclusion criteria and ethnic composition of the study population may explain this discrepancy. In our study, the prevalences of metronidazole resistant \textit{H. pylori} of the autochthonic and allochthonic population corresponded with those of the different geographic origins of the patients, being 16\% and 30\%, respectively (n.s.).

The prevalence of primary clarithromycin resistant \textit{H. pylori} is low in this patient population and therefore does not affect the eradication rate as the eradication rates were identical in patients colonised with metronidazole resistant \textit{H. pylori} and patients infected with susceptible \textit{H. pylori}. These results are in concordance with those earlier reported by others.\textsuperscript{18,19} In contrast, some studies show a difference in the outcome of metronidazole containing triple therapies when given to patients infected with metronidazole resistant \textit{H. pylori} or to patients colonized with metronidazole susceptible \textit{H. pylori}.\textsuperscript{12,18,20,21}

Compliance is an other important factor for a successful \textit{H. pylori} eradication.

In general compliance increases inversely proportional to the duration of the therapy. The compliance was equally high (100\%) with the three \textit{H. pylori} eradication treatments in this study. This might be the result of the attention paid to health education, instruction of the patients and the very low number of serious adverse events caused by the treatments as reported by the patients.

The cost of eradication therapy is affected by the dose of the drugs and the duration of the therapy. In the Netherlands, a 7 days therapy with dosages twice daily omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg will reduce the cost for the \textit{H. pylori} eradication therapy by 22\%, when compared to the same therapy, but with a higher dose of clarithromycin (500 mg) and metronidazole (500 mg). Reducing the duration of the therapy to 4 days will further decrease the cost of the original 7 days therapy by 55\%.

All patients of this study had either active or a documented history of ulcer disease. It would be interesting to see whether these good eradication rates can also be obtained with functional dyspepsia. The eradication rates in studies with functional dyspepsia as well as patients with
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ulcer disease are lower than in studies with solely patients with ulcer disease.\textsuperscript{22} It is assumed that theoretically cagA\textsuperscript{+} \textit{H. pylori} which relates significantly more with the presence of ulcer disease than functional dyspepsia may be more susceptible to antimicrobials. However, in vitro experiments do not support this assumption. An alternative explanation may be that cagA\textsuperscript{+} \textit{H. pylori} grow faster thereby being more susceptible to bactericidal antimicrobials in vivo.\textsuperscript{23}

More research in duration and dosages of drugs in \textit{H. pylori} eradication therapies is warranted.

In conclusion, all three anti-\textit{H. pylori} treatments differing in duration were well-tolerated and revealed 100\% \textit{H. pylori} eradication rates even in a population with moderately prevalent metronidazole resistance.

In patients with ulcer disease 4 days \textit{H. pylori} eradication regimen (omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg) is highly efficacious and is as effective as same regimens of longer duration.

References

Chapter 4


