The treatment of helicobacter pylori infection and its sequelae with emphasis on nitroimidazole resistance
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Chapter 7

The influence of metronidazole resistance on the efficacy of two one-week, ranitidine bismuth citrate containing, triple therapy regimens for Helicobacter pylori infection.

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Abstract.

Background: Data on the influence of metronidazole resistance on the efficacy of ranitidine bismuth citrate (RBC) based triple therapy regimens are scarce. Therefore, two consecutive studies were performed.

Methods: In the first study, patients with a culture proven *Helicobacter pylori* infection were treated with RBC 400 mg, metronidazole 500 mg, and clarithromycin 500 mg, all bid for one week (RMC). In the second study amoxicillin 1000 mg was substituted for clarithromycin (RMA). Susceptibility testing for metronidazole was performed with the E-test. Follow-up endoscopy was performed after ≥4 weeks. Antral biopsy samples were taken for histology, urease test, and culture and corpus samples for histology and culture.

Results: 112 patients, 53 males, age 55±14, (39 duodenal ulcer, 7 gastric ulcer and 66 gastritis) were treated with RMC and 89 patients, 52 males, age 58±15, (23 duodenal ulcer, 7 gastric ulcer and 59 gastritis) were treated with RMA. For RMC ITT eradication results were 98% (59/60, 95%CI: 91-100%) and 95% (20/21, 95%CI: 76-100%) for metronidazole susceptible and resistant strains, respectively (p=0.45). For RMA these figures were 87% (53/61, 95%CI: 76-94%) for metronidazole susceptible strains and 22% (2/9, 95%CI: 3-60%) for resistant strains (p=0.0001).

Conclusion: Both regimens are effective in metronidazole susceptible strains. But in contrast to the amoxicillin containing regimen, the one containing clarithromycin is also effective in resistant strains.
**Introduction.**

Metronidazole is frequently used in eradication regimens for *Helicobacter pylori* (*H. pylori*) infections (1). Susceptibility of *H. pylori* to metronidazole is one of the main factors determining the efficacy of these metronidazole containing treatment regimens (2-4). As metronidazole resistance seems to be increasing in different parts of the world, highly effective regimens for metronidazole resistant *H. pylori* strains are urgently needed (5-11).

In a recent randomised study, we have shown that a one-week regimen with ranitidine bismuth citrate (RBC), clarithromycin, and metronidazole is highly effective in eradicating *H. pylori*. Only a small number of patients in this study were infected with a metronidazole resistant strain, but the regimen seemed to be equally effective in these patients (12). In view of this experience, it was decided to enlarge the number of patients in order to determine the influence of metronidazole resistance on the efficacy of this regimen.

As it is unknown if the combination of RBC and clarithromycin is essential for this effect we substituted amoxicillin for clarithromycin in another open study.

**Methods.**

Patients aged 18 and above with a culture proven *H. pylori* infection were eligible. Reasons for exclusion were resective gastric surgery, gastric cancer, other major diseases, pregnancy or lactation, known allergy to one of the study medications, and the need for bismuth, protonpump inhibitors (PPI), or antibiotics between endoscopy and the start of trial medication. All patients gave informed consent.

At each endoscopy four antral biopsy specimens were taken: one for culture, one for rapid urease testing, and two for histological examination. Moreover, two corpus biopsy specimens were taken prior to treatment (both for histology) and three at follow-up (one for culture and two for histology). A home made urease test was used as described previously (13). Histological examination was performed according to the Sydney classification using the haematoxylin-eosin stain (14). Culture was performed as described previously (15). Susceptibility to clarithromycin and metronidazole was determined using the E-test (AB Biodisk, Solna, Sweden). A strain was considered metronidazole resistant when the minimal inhibitory concentration (MIC) was >8 µg/ml and clarithromycin resistant when the MIC was >2 µg/ml (16). Susceptibility for
amoxicillin was tested with a disk diffusion method, using a 2 µg disk (Becton Dickinson, Cockeysville, MD, USA). Strains with an inhibition zone of <10 mm were regarded resistant.

In the first study patients were treated with RBC (Pylorid™, GlaxoWellcome BV, Zeist, the Netherlands) 400 mg, metronidazole 500 mg, and clarithromycin (Klacid™, Abbot B.V., Amstelveen, the Netherlands) 500 mg, all bid for one week (RMC). In the second study the same one-week regimen was used except that amoxicillin (Flemoxin solutab™, Yamanouchi Pharma B.V., Leiderdorp, the Netherlands) 1000 mg, bid was substituted for clarithromycin (RMA).

One to seven days after the end of treatment compliance to the prescribed treatment was checked and general tolerance to the treatment was assessed as described previously (17).

Follow-up endoscopy was performed at least 4 weeks after the end of treatment. A patient was considered successfully treated if all biopsy-based tests were negative and a treatment failure if culture or at least two other tests were positive. If only one of these other tests suggested the presence of *H. pylori*, a 13C-urea breath test was performed as described previously (13), and considered conclusive. Per protocol (PP) and intention to treat (ITT) analysis was performed as recommended by the European *Helicobacter pylori* Study Group (18). Eradication rates were compared using the Fisher's exact test and a p < 0.05 was considered significant.

**Results.**

One hundred and twelve patients were treated with RMC; 52 of them took part in a randomised controlled study published elsewhere (12). Subsequently, 89 patients were treated with RMA. Gender, age, and endoscopic diagnosis of these patients are summarised in table 1.

In 46 patients susceptibility testing of the infecting *H. pylori* strain failed because of fungal overgrowth or death of the strain. Metronidazole resistance was observed in 31 strains and clarithromycin resistance in 4 strains (all 4 treated with RMC). Combined resistance was observed in one of these strains. All strains tested were susceptible to amoxicillin (figures 1 and 2).

Compliance to the medication was good as all patients took >90% of the study medication. Both treatment regimens were well tolerated (table 2). Thirty-four patients (31%, 95% CI: 23-40%) treated with RMC and 18 patients (20%, 95% CI: 12-30%)
Table 1. Characteristics of the patients treated with two ranitidine bismuth citrate based triple therapy regimens.

<table>
<thead>
<tr>
<th></th>
<th>RBC CLA MET</th>
<th>RBC AMO MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>112</td>
<td>89</td>
</tr>
<tr>
<td>Sex (men : women)</td>
<td>53 : 59</td>
<td>52 : 37</td>
</tr>
<tr>
<td>Age (mean ± standard dev.)</td>
<td>55 ± 14</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Duodenal Ulcer</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td>Gastritis</td>
<td>66</td>
<td>59</td>
</tr>
</tbody>
</table>

RBC, CLA, MET, and AMO represent ranitidine bismuth citrate, clarithromycin, metronidazole, and amoxicillin, respectively.

treated with RMA experienced significant side effects, but all patients completed the course.

A total of 16 patients were excluded from the PP analysis (9 treated with RMC and 7 treated with RMA). Seven patients refused follow up endoscopy (three of them were willing to undergo a $^{13}$C-urea breath test). In one patient a lungcarcinoma was diagnosed and endoscopy was considered inappropriate. Nine patients used extra antibiotics between the start of treatment and the follow up endoscopy (one of them was also among those refusing the second endoscopy and undergoing a breath test instead).

In the ITT analysis patients without an objective endpoint (endoscopy or $^{13}$C-urea breath test) were considered treatment failures (figures 1 and 2).

In 8 patients (6 treated with RMC) histologic examination after treatment still suggested the presence of *H. pylori* in low density (grade 1) in either the antrum or corpus specimen, while all the other biopsy based tests were negative. In another patient treated with RMA, only the urease test suggested treatment failure. In all these patients, however, the $^{13}$C-urea breath test was negative. Therefore, these patients were considered successfully treated.
**Figure 1.** Flow chart presenting the results of triple therapy with ranitidine bismuth citrate, clarithromycin and metronidazole. Met and Cla represent metronidazole and clarithromycin, respectively. S and R represent susceptible and resistant, respectively. Susc. unknown represents susceptibility unknown.

Treatment results are summarised in figures 1 and 2. In the patients treated with RMC there was no significant difference in eradication rate between metronidazole susceptible and resistant *H. pylori* strains (susceptible vs resistant: 98% vs 95%, ITT, p = 0.45). Furthermore, all 4 clarithromycin resistant strains were successfully eradicated. In the patients treated with RMA, however, efficacy dropped significantly when patients infected with a metronidazole resistant strain were compared to those infected with a metronidazole susceptible strain (resistant vs susceptible: 22% vs 87%, ITT, p = 0.0001).
Figure 2. Flow chart presenting the results of triple therapy with ranitidine bismuth citrate, amoxicillin and metronidazole. Met and Cla represent metronidazole and clarithromycin, respectively. S and R represent susceptible and resistant, respectively. Susc. unknown represents susceptibility unknown.

Data about secondary resistance in the 15 strains escaping eradication are shown in table 3. Neither resistance to clarithromycin nor resistance to metronidazole was induced in the 2 strains escaping RMC. In all of the 4 metronidazole susceptible strains in which the RMA regimen failed, however, metronidazole resistance was observed after treatment. No secondary resistance to amoxicillin was observed.
Table 2. Severity of side effects of two ranitidine bismuth citrate based triple regimens according to the judgement of the patient (17).

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>RBC CLA MET</th>
<th>RBC AMO MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>A No side effects</td>
<td>11 (10%)</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>B Slight discomfort, not interfering</td>
<td>66 (59%)</td>
<td>52 (58%)</td>
</tr>
<tr>
<td>C Moderate side effects, sometimes</td>
<td>21 (19%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>D Severe side effects, working not</td>
<td>13 (12%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>E Side effects severe enough to</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>discontinue treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Good tolerance (groups A-B) 77 (69%) 71 (80%)
Poor tolerance (groups C-E) 34 (31%) 18 (20%)

RBC, CLA, MET, and AMO represent ranitidine bismuth citrate, clarithromycin, metronidazole, and amoxicillin, respectively.

Discussion.
Confirming the results of other investigators, the first part of our study shows that triple therapy with RBC, clarithromycin, and metronidazole effectively eradicates *H. pylori* (19-28). Furthermore, the study shows that metronidazole resistance does not influence the efficacy of RMC to a significant degree. In that aspect our data confirm the preliminary results of Bardhan et al. who found an PP eradication rate of 100% (*n* = 33) in patients infected with a metronidazole susceptible strain and of 90% (*n* = 10) in patients infected with a resistant strain, (*p* = 0.25, Fisher's exact test) (20). It is remarkable that in our study all 4 clarithromycin resistant strains were successfully eradicated.

In contrast, the second part of our study shows that metronidazole resistance significantly diminishes the efficacy of RMA. This regimen is effective in patients
Table 3. The pre- and posttreatment susceptibility to antibiotics of the strains persisting after treatment two ranitidine bismuth citrate based triple regimens.

<table>
<thead>
<tr>
<th>n</th>
<th>Pretreatment</th>
<th>Treatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLA</td>
<td>MET</td>
<td>CLA</td>
</tr>
<tr>
<td>1</td>
<td>S</td>
<td>R</td>
<td>RBC</td>
</tr>
<tr>
<td>1</td>
<td>?</td>
<td>?</td>
<td>RBC</td>
</tr>
<tr>
<td>4</td>
<td>S</td>
<td>S</td>
<td>RBC</td>
</tr>
<tr>
<td>6</td>
<td>S</td>
<td>R</td>
<td>RBC</td>
</tr>
<tr>
<td>1</td>
<td>S</td>
<td>R</td>
<td>RBC</td>
</tr>
<tr>
<td>1</td>
<td>?</td>
<td>?</td>
<td>RBC</td>
</tr>
<tr>
<td>1</td>
<td>?</td>
<td>?</td>
<td>RBC</td>
</tr>
</tbody>
</table>

n represents the number of cases, RBC, CLA, MET, and AMO represent ranitidine bismuth citrate, clarithromycin, metronidazole, and amoxicillin, respectively. S and R represent susceptible and resistant, respectively. Resistance to amoxicillin was not observed.

infected with a metronidazole susceptible strain, but efficacy is low in those infected with a resistant strain. The only available study using a similar one-week regimen (RBC 400 mg, amoxicillin 1000 mg, and tinidazole 500 mg, all bid) reported an eradication rate of 61%, but susceptibility testing was not performed (28).

It is noteworthy that metronidazole resistance does not influence the efficacy of the first regimen but strongly diminishes the efficacy of the second regimen, where amoxicillin was substituted for clarithromycin.

It is acknowledged that there are scientific limitations in comparing the results from two consecutive studies. However, our studies had a similar design, were performed in the same rural area, and gender, age, and endoscopic diagnoses of the patients were comparable. Therefore, another explanation is suggested.

If the various anti-

H. pylori regimens using one of these drugs are considered, clarithromycin seems to be more effective than amoxicillin (1). Furthermore, several in-
vitro studies have shown synergy between RBC and clarithromycin (29-31) while the in-vitro interaction of RBC and amoxicillin is additive only (35). Therefore, it is to be expected that the combination of RBC with clarithromycin will be the more effective one in-vivo as well. Several studies using one-week dual therapy with RBC and clarithromycin have shown ITT eradication rates of 75-87% (20,32-34). Recently, it was shown that this combination is as effective as RMC (20).

Consequently, it is possible that metronidazole can be omitted. On the other hand, when amoxicillin is used instead of clarithromycin, the regimen loses efficacy and metronidazole becomes an essential component of the regimen. In that case metronidazole resistance becomes far more significant. Based on these considerations it is suggested that the significance of metronidazole resistance is dependent on the overall efficacy of the treatment regimen. The experience with quadruple therapy supports this hypothesis. The efficacy of this regimen increases with prolongation of treatment duration and the longer the duration the less the significance of metronidazole resistance (3). If a quadruple regimen is given for one-week, metronidazole resistance still decreases efficacy somewhat (37), but this influence is absent when it is given for 12 days (38). The one-week regimen with RMC is, in this regard, comparable to prolonged quadruple therapy. Our regimen, however, is less complex, as all medication is given bid.

It could be objected that the combination of metronidazole and clarithromycin in RMC is disadvantageous, as secondary resistance to both clarithromycin and metronidazole could be induced (36). Our study, however, shows that RMC is highly effective, even in the presence of metronidazole resistance. Moreover, although our data are limited, in the few cases escaping treatment no secondary resistance was observed. In the less effective RMA regimen, however, secondary resistance to metronidazole was observed in all of the four previously metronidazole susceptible strains.

In summary, this study shows that RBC and metronidazole, in combination with either amoxicillin or clarithromycin is effective in metronidazole susceptible strains. In contrast to the amoxicillin containing regimen, the one containing clarithromycin is also effective in metronidazole resistant strains.

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