Efficacy of metronidazole-based triple therapy on eradicating H. pylori positive peptic ulcers in mainly Saudi patients

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ABSTRACT

Objectives: To evaluate the short-term efficacy of triple antibiotics on eradicating H. pylori from peptic ulcer patients. Design: Prospective study. Patients and methods: Peptic ulcer patients of both sexes were included if they were H. pylori positive on culture and/or histology and were aged between between 18-75 years. Patients were excluded if they had severe coagulopathy, if the females were pregnant and if antibiotics or non-steroidal anti-inflammatory drugs had been recently used. All patients received a combination of metronidazole 500 mg PO t.i.d., amoxicillin 500 mg PO q.i.d., both for 2 weeks and bismuth subcitrate colloidal 120 mg PO q.i.d. for 4 weeks, in addition to ranitidine 300 mg PO at night for 6 weeks. Eradication of H. pylori was defined as absence of the organism in both histology and culture 6 weeks after completing triple therapy. H. pylori susceptibility was performed using the disc diffusion method. Results: Forty-nine patients; 38 males, mean age 41.4 years and 11 females, mean age 40.3 years were included. Eighty-five percent of peptic ulcers had healed by the end of the study period. However, only 49% of H. pylori was successfully eradicated. Overall metronidazole resistance was encountered in 45.7% of H. pylori isolate. Females harbored resistant strains more frequently than males, 77.8% versus 34.6%, respectively (p=0.05). Conclusions: Metronidazole based triple therapy has a low success rate which is most likely secondary to H. pylori resistance.

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Successful eradication of H. pylori from a duodenal ulcer patient reduces the frequency of ulcer relapse. On the other hand persistent H. pylori infection is the main cause of duodenal ulcer recurrence. Several therapeutic regimens have been used successfully to eradicate H. pylori with variable results. Triple therapy consisting of bismuth sub salicylate, tetracycline or amoxicillin combined with metronidazole, or omeprazole combined with clarithromycin and amoxicillin have been shown to be the most effective regimens. The major factors influencing the rate of H. pylori eradication are patient compliance and H. pylori sensitivity to metronidazole. To test the efficacy of metronidazole-based triple therapy in our population we prospectively conducted an open trial on patients with H. pylori positive peptic ulcers.

Patients and methods. This prospective trial was carried out on patients with H. pylori positive peptic ulcers seen at two university hospitals (King Khalid University Hospital and King Abdulaziz University Hospital, Riyadh). Entry criteria included H. pylori positive duodenal ulcer, gastric ulcer and at least three duodenal or gastric erosions. Age between 18-75 years. Exclusion criteria included severe coagulopathy, pregnancy, recent antibiotics used and current use of non-steroidal anti-inflammatory drugs. Patients underwent upper gastrointestinal endoscopy at entry and 6 weeks after completing triple therapy. During endoscopy three antral biopsies were obtained. One was placed in 0.9% normal saline and immediately transported for bacteriology culture. The other two were placed in 10% buffered formalin solution.

Histology. Antral biopsies were sectioned and stained with hematoxylin and eosin in all specimens and some with the Warthin Starry technique to identify the organism.
**Bacteriology.** The specimens placed in normal saline were bisected using sterile forceps. Freshly cut surface was inoculated into sheep blood agar and incubated in a microaerophilic atmosphere at 37 °C. Details were described elsewhere.13,14 H. pylori was considered positive if either histology or bacteriology examination revealed organisms. Eradication of H. pylori was defined as absence of the organisms in both histology and culture reports 6 weeks after completing triple therapy. H. pylori sensitivity was carried out in 35 isolates to metronidazole (5 μg) using disc diffusion technique. The isolates were obtained before drug therapy. The 5 μg metronidazole disk was placed in the center of the brucella agar plate streaked with cotton wool saturated with H. pylori strain and was incubated at 37 °C in a microaerobic atmosphere for 72 hours. An inhibition zone of 25 mm diameter around the disc was defined as metronidazole sensitivity.

**Medication.** All patients were given ranitidine 300 mg PO at night for 6 weeks. In addition, a combination of metronidazole 500 mg PO t.i.d., amoxicillin 500 mg PO q.i.d. for 14 days and bismuth subcitrate colloidal 120 mg PO q.i.d. for 4 weeks. Compliance was assessed by pill counting. Only patients who consumed 80% of medication were allowed to complete the study. Males and females were compared with regard to age, response to treatment and metronidazole sensitivity pattern. Saudi and non-Saudi patients were also compared regarding age, sex and rate of H. pylori eradication. Differences were compared by means of the chi-square and Fischer exact test; p-value <0.05 was considered significant.

**Results** Out of the 54 patients included in this study, 5 were subsequently excluded from analysis due to failure to attend for the second endoscopy (n=3) or if they had ingested less than 80% of medication (n=2). All the remaining patients ingested 100% of the regimen except 3 male patients. Metronidazole was missed in two occasions by 1 patient. The other 2 patients discontinued bismuth subcitrate colloidal in the last day of treatment due to stool color change. Forty-nine patients completed this study; 38 males mean age 41.411 and 11 females mean age 40.315 years. Seventy-one point four percent of the study population were Saudi patients.

Table 1 shows demographic data endoscopic diagnoses at entry and healing rate of peptic ulcer and H. pylori eradication rate. Duodenal ulcers and erosions constituted the majority (76.4%) of peptic ulcer disease encountered in this study. Eight-three point seven percent of peptic ulcers were healed at the end of the treatment period. However, only 49% of H. pylori were successfully eradicated. The rate of eradication was superior in males compared to females 55% and 27%, respectively. However, the difference was not significant.

Table 2 compared age, sex and H. pylori eradication rate between Saudi and non-Saudi patients. There was no significant difference between the two groups.

In vitro metronidazole sensitivity was performed on 35 H. pylori isolates using disc diffusion technique (26 isolates were from males). Sixteen strains (45.7%) were resistant; 9 in males and 7 in females. Resistant strains were more frequently found in females (77.8%) compared to males (34.6%) p=0.03.

**Discussion** Recently the National Institutes of Health Consensus on H. pylori recommended that all patients with gastric or duodenal ulcers who are infected with H. pylori should be treated with anti microbial regardless of whether they are suffering from the initial presentation of the disease or from a recurrence.15

Available data suggests that metronidazole is a key drug in the triple therapy.16 A combination of metronidazole, bismuth subsalicylate and tetracycline or amoxicillin has yielded one of the best eradication rates of H. pylori approaching 90% in the Western population.15,18

**Table 2 - Treatment response in Saudi and non-Saudi patients**

<table>
<thead>
<tr>
<th></th>
<th>Saudi</th>
<th>Non-Saudi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age/years (SD)</td>
<td>41</td>
<td>(13.8)</td>
<td>41.6</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>26/19</td>
<td></td>
<td>12/2</td>
</tr>
<tr>
<td>H. pylori negative/total</td>
<td>18/35</td>
<td>(51.4%)</td>
<td>6/14</td>
</tr>
<tr>
<td>H. pylori negative (males)</td>
<td>15/26</td>
<td>(57.7%)</td>
<td>6/12</td>
</tr>
<tr>
<td>H. pylori negative (females)</td>
<td>3/9</td>
<td>(33.3%)</td>
<td>0/2</td>
</tr>
</tbody>
</table>

*P = 0.2 N = Non-Saudis
S = Saudis No = Number
**Some patients had more than one endoscopic lesions
More recently, omeprazole combined with clarithromycin and amoxil for 10 days has been shown to be highly effective in eradicating *H. pylori*. Moreover, the side effects of such regimen are mild.3,12,19

To the best of our knowledge, this is the first prospective trial which has looked into the efficacy of triple therapy consisting of metronidazole, amoxicillin and bismuth subcitrate colloidal and assessed the in vitro sensitivity of *H. pylori* isolates to metronidazole in a large population of Saudi patients. Metronidazole based triple therapy was chosen in our study because of: (a) the regimen has been tested by many investigators and all have consistently reported a high success rate of *H. pylori* eradication; 3,5,6,8,18 (b) we wanted to look at metronidazole sensitivity in our population and (c) these drugs are available in our hospitals.

Our results showed that only 49% of *H. pylori* strains have been successfully eradicated six weeks after triple drug therapy. Moreover, the failure rate was higher in females (72.7%) compared to males (44.7%). However, the difference was not statistically significant.

Metronidazole resistance (45.7%) is probably the most important reason accounting for failure to eradicate *H. pylori* in our study population. The other reason could have been drug compliance. Graham et al were the first group to examine the factors responsible for a low rate of eradication of *H. pylori* and found that failure to take the prescribed medication was the variable that best predicted a poor result. Furthermore, they also found that patients who ingested ≥ 60% of their therapy had 96% success rate of *H. pylori* eradication compared with 69% of those who took < 60%.12

All of our study population ingested more than 90% of the prescribed drugs and it seems probable that metronidazole resistance plays a major role in the success rate of *H. pylori* eradication in our population and therefore is best avoided.

Metronidazole resistance rate varies among the population studied and the frequency ranges between 27% and 90%. 16,17,20,22

Development of metronidazole resistance is either primary or related to previous drug exposure.10,23-25 In this study females harboured a significantly higher percentage of metronidazole resistance *H. pylori* strains than males p=0.03, which is similar to previous authors’ experiences. 16,17,21 This could be attributed to more frequent requirement of metronidazole for gynecological diseases16,21 and may explain the higher failure rate of eradication among female patients.

**Conclusion** Metronidazole-based triple therapy has a low *H. pylori* eradication rate. The most likely explanation is metronidazole resistant which is more significant in female patients. It is worth studying *H. pylori* sensitivity pattern in our population before recommending antibiotic combination.

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**References**
