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Original article

Improving the standard sequential treatment of *Helicobacter pylori* with either extended treatment or by adding bismuth

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ABSTRACT

Background and study aims: Standard sequential treatment for *Helicobacter pylori* (*H. pylori*) eradication has less success because of increasing clarithromycin resistance. Extended treatment and bismuth containing regimens were, therefore, investigated.

Patients and methods: Consecutive *H. pylori*-positive patients with dyspepsia were randomly allocated to one of the three sequential regimens: The first group was given lansoprazole 30 mg b.i.d. plus amoxicillin 1 g b.i.d. for the first 5 days, followed by lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and metronidazole 500 mg t.i.d. for the second 5 days (standard sequential, SS). The second group was given the same regimen but for 7 + 7 days instead of 5 + 5 days (extended sequential, ES). In the third group, colloidal bismuth 600 mg b.i.d. was added to the second regimen for 14 days (extended sequential + bismuth subcitrate, ES + B). Urea breath test or histology was performed before enrolment and 6 weeks after the end of treatment to detect *H. pylori*.

Results: A total of 280 patients were included in the study. Per-protocol eradication rates were 62% (56/90), 72% (56/78), and 75% (54/72) in patients who received SS, ES, and ES + B regimens, respectively. Moreover, intention-to-treat eradication rates were 53% (56/104), 62% (56/90) and 62% (54/86), respectively. The differences in eradication rates between the groups were not statistically significant.

Conclusion: Although prolonging of the sequential treatment to 14 days may be considered, addition of bismuth to the regimen is of no avail.

Introduction

Helicobacter pylori infection is considered the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. Even with 30 years of experience in *H. pylori* treatment, however, the ideal regimen to treat this infection is yet to be found.

Sequential therapy consisting of a proton pump inhibitor (PPI) plus amoxicillin for 5 days, followed by a PPI plus clarithromycin and tinidazole (or metronidazole) for another 5 days, has been shown to be more effective than the standard triple therapy as the first-line treatment in Italy [1–4]. Sequential regimen would be a promising alternative first-line therapy.

Sequential regimen was largely heralded as being able to overcome clarithromycin resistance. Recent studies have shown that eradication rates can be influenced by clarithromycin resistance, and in the presence of clarithromycin resistance mutation, eradication rates decrease to 65% [5]. A study from Turkey, where eradication rates are low, showed 78% eradication with sequential therapy versus 53% with standard triple therapy based on a per-protocol (PP) analysis [6]. Thus, standard 5-day sequential therapy could not achieve beyond the 80% intention-to-treat (ITT) eradication rate, which is considered to be the minimal acceptable level according to the Maastricht guidelines [7].

Data have shown that bismuth subsalicylate is hydrolysed in the gut to oxychloride and salicylic acid and less commonly to bismuth hydroxide. Bismuth oxychloride and bismuth hydroxide are both considered to have bactericidal effects [8].

The aim of this study was to evaluate the success of sequential therapy and whether prolonging the treatment duration to 14 days or adding bismuth to the 14-day treatment improves eradication rates.

Patients and methods

Patients who visited the Gastroenterology Clinics of Izmir Ataturk Training and Research Hospital between May 2011 and May 2012 for upper gastrointestinal symptoms were tested for *H. pylori*

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infection, and those who were *H. pylori* positive were recruited. Pre-enrolment procedures included urea breath test (UBT) or biopsy of gastric mucosa, where the presence of *H. pylori* was assessed by histological examination. Endoscopy was performed if alarming symptoms were present or in new-onset dyspepsia after the age of 45. Blood samples were obtained for routine laboratory tests including complete blood count, renal function, and liver biochemical tests to ascertain that there were no abnormal results that would preclude entry into the trial.

Exclusion criteria included the following: (1) previous attempts at *H. pylori*-eradication therapy; (2) intake of antibiotics, bismuth, or PPIs within the last 4 weeks; (3) patients with a history of allergy to the medications used; (4) patients who underwent previous gastric surgery; (5) coexistence of serious concomitant illness (decompensated liver cirrhosis, uraemia, etc.); and (6) pregnancy or lactation.

Participants were randomly assigned to one of three treatment groups:

1) standard sequential therapy of lansoprazole 30 mg b.i.d. plus amoxicillin 1000 mg b.i.d. for the first 5 days and lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and metronidazole 500 mg t.i.d. for the following 5 days; (standard sequential, SS group);
2) extended sequential therapy of lansoprazole 30 mg b.i.d. plus amoxicillin 1000 mg b.i.d. for the first 7 days and lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and metronidazole 500 mg t.i.d. for the following 7 days; (extended sequential, ES group);
3) extended sequential plus bismuth therapy of lansoprazole 30 mg b.i.d., amoxicillin 1000 b.i.d. mg, and bismuth subcitrate 600 mg b.i.d. for the first 7 days and lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., metronidazole 500 mg t.i.d., and bismuth 600 mg b.i.d. for the following 7 days. (extended sequential plus bismuth, ES + B group).

Eradication rates were assessed by ^{13}C-UBT or a follow-up endoscopy (in case of gastric ulcer) and histological examination 6 weeks after the end of the regimen. Eradication was defined as a negative result of histology or UBT.

Written informed consent was obtained from all patients, and the study was approved by the local ethical committee.

Histologic examination

Two specimens of gastric biopsies were obtained from the lesser curvature site of the antrum and the lesser curvature site of the corpus for histological examination, fixed in 10% buffered formalin, embedded in paraffin, and sectioned. The sections were stained with haematoxylin and eosin and a modified Giemsa stain to observe the presence of curved rod-shaped bacteria on the mucosal surface. Biopsy specimens were assessed by histopathologists who were blinded to the patient's status.

Urea breath test

The UBT was performed as described in previous studies. The cut-off value was set at 4.8 of d13-CO_2 [9]. The staff who performed the test were also blinded to the *H. pylori* status of the patients.

Statistical analysis

ITT and PP analyses were used to assess the eradication rates of *H. pylori* in the three groups. The eradication rates and frequencies of adverse effects were compared using the chi-squared test. The significance level was set at $p < 0.05$. Patients were randomly allocated to the three treatment groups using a random numbers table.

Results

A total of 280 subjects admitted to the outpatient clinic for dyspeptic symptoms were included in the study, and 240 patients were able to complete the study. The treatment groups did not differ in baseline demograph and anthropometric data at entry and during follow-up (Table 1). The mean ages of patients in SS, ES, and ES + B groups were 46.4 ± 45, 50.5 ± 39, and 50.8 ± 36, respectively, and the number of males was 28 (26%), 24 (26%), and 34 (39%), respectively. Sixty endoscopies were performed at the beginning of the study; 6 patients had duodenal ulcers and 4 patients had gastric ulcers.

Seven patients in the SS group, 7 patients in the ES group, and 9 patients in the ES + B group were excluded from the study because of protocol violation. Moreover, 7 patients in the SS group, 5 patients in the ES group, and 5 patients in the ES + B group did not return for control. Treatment was discontinued in three patients in the SS group and 2 each from the ES and ES + B groups because of adverse drug effects. Patients with adverse drug reactions were included in the protocol violation group. In total, 90 patients in the SS group, 78 patients in the ES group, and 72 patients in the ES + B group completed their regimens and made up the PP population.

The cumulative "PP" and "ITT" eradication rates were 69.1% (166/240) and 59.2% (166/280) for all patients, respectively. *H. pylori* eradication was achieved in 56 of 104 (ITT) patients in the SS group (PP eradication = 62.2% and ITT eradication = 53.8%), 56 of 90 (ITT) patients in the ES group (PP eradication = 71.7% and ITT eradication = 62.2%), and 54 of 86 (ITT) patients in the ES + B group (PP eradication = 75% and ITT eradication = 62.7%).

Table 1
Number of patients with regard to treatment groups and treatment success and their demograph characteristics.

	Total number of patients	Standard sequential	Extended sequential	Extended sequential plus bismuth
Number of patients (ITT)	280	104	90	86
Number of patients (PP)	240	90	78	72
Number of eradication-positive patients	166	56	56	54
Mean age		46.4 ± 45	50.5 ± 39	50.8 ± 36
Number of males		28 (31%)	24 (30%)	34 (47%)

Table 2
H. pylori eradication rates.

	Standard sequential	Extended sequential	Extended sequential plus bismuth	Significance
Intention to treat	53.8% 56/104	62.2% 56/90	62.7% 54/86	$p > 0.05$
Per protocol	62.2% 56/90	71.7% 56/78	75% 54/72	$p > 0.05$

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