High-dose dual therapy is effective as first-line treatment for Helicobacter pylori infection

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ABSTRACT

Background/Aims: Although many regimens, including quadruple, sequential, and concomitant treatment, are used and recommended as first-line or rescue therapies for Helicobacter pylori infection, eradication rates are still below 90% in intention-to-treat analyses. Treatment protocols with substantially high eradication rates and low antibiotic resistance are needed. In this study, we investigated the efficacy of high-dose dual therapy as first-line treatment in a Turkish population.

Materials and Methods: All patients underwent upper gastrointestinal endoscopy for the initial H. pylori status because of dyspeptic symptoms. All patients received a 14-day, high-dose dual therapy comprising rabeprazole (20 mg t.i.d.) and amoxicillin (1 g t.i.d.) for H. pylori eradication. H. pylori stool antigen tests of eradication were administered to all participants at least 4 weeks after the completion of the treatment.

Results: The high-dose dual therapy demonstrated a 91.3% rate of successful eradication of H. pylori infection. Per-protocol success was 94.4% among female patients (n=51) and 89.6% among male patients (n=86); in terms of gender, the differences were not significant (p=0.310). No side effects were observed during the study in any patient. Six other patients did not take adequate doses of the treatment protocol.

Conclusion: High-dose dual therapy with rabeprazole and amoxicillin was highly effective and well tolerated as a first-line therapy for H. pylori eradication.

Keywords: Helicobacter, high dose dual therapy, rabeprazole

INTRODUCTION

Helicobacter pylori, a gram-negative and microaerophilic bacterium, is present in more than half of the world's population, especially in developing countries. *H. pylori* infection leads to various nonspecific gastrointestinal symptoms and is a risk factor for serious health conditions such as peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer (1, 2). Thus the eradication of *H. pylori* infection is important, especially in patients with other risk factors for those conditions. Clarithromycin-containing triple therapy has been recommended as a first-line therapy (3). However, the effectiveness of a *H. pylori* eradication regimen varies in different areas, and the infection remains a challenge because of increasing antibiotic resistance.

Although many regimens, including quadruple, sequential, and concomitant treatment, are used and recommended as a first-line or rescue therapies, eradication rates are below 90% in intention-to-treat analysis (4). Failure to eradicate the infection also increases the development of secondary antibiotic resistance when first-line therapy fails (5,6). Therefore, antimicrobial susceptibility testing has been suggested in areas of high antibiotic resistance after the failure of first-line treatment. However, this test is not available in most centers and is not useful in clinical practice. To solve this problem, treatment protocols with substantially high eradication rates and low antibiotic resistance are needed. Although regimens containing clarithromycin, metronidazole, and levofloxacin are initially effective, the eradication rates of these antibiotics decrease over time as a result of acquired resistance (7). Amoxicillin, which is a β-lactam antibiotic, is the cornerstone of treatment for *H. pylori* and is used in almost all current therapeutic eradication regimens. It is also one of the antibiotics most commonly used for the treatment of various infections in clinical practice (8). Despite such widespread use, more than 1% of *H. pylori* infections are resistant to amoxicillin (9, 10).

Deeper gastric acid suppression with a combination of high-dose proton pump inhibitors (PPIs) and amoxicillin, known as "dual therapy," was one of the most popular therapies in the mid-1990s, especially in Europe (11).

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However, controversial results in subsequent studies reduced its impact on clinical practice. In recent years, dual therapy has been reconsidered for the treatment of *H. pylori* infection by researchers from various regions (12). Despite the different results, this regimen appears to be promising as potential therapy for *H. pylori.* The discrepancy in results can be explained by the difference in doses and frequencies, as well as PPI preferences.

In this study, we investigated the efficacy of high-dose dual therapy as first-line treatment of *H. pylori* infection in the Turkish population. We also aimed to show the compliance with and side effects of this regimen.

MATERIALS AND METHODS

Study population

This study was designed and conducted among patients in the gastroenterology outpatient clinic from May 2017 to October 2018 in Gulhane School of Medicine, Ankara, Turkey. This study was approved by the local ethics committee (23 December 2013, no. 2875). All patients had dyspeptic symptoms and underwent upper gastrointestinal endoscopy to evaluate initial *H. pylori* status. Diagnosis of *H. pylori* was based on the presence of positive results of both histologic and rapid urease tests. Two biopsy specimens for the rapid urease test and four biopsy specimens for histopathologic examination were taken from the corpus and antrum in each patient.

A total of 268 patients between the ages of 18 and 70 years who had *H. pylori* infection were initially enrolled in the study. However, patients who did not undergo the *H. pylori* stool antigen (HpSA) test at least 4 weeks after eradication therapy and who did not complete the 4-week period without treatment were not included in this study. The final number of patients included in the study was 150. Exclusion criteria were as follows: (a) having undergone previous *H. pylori* eradication therapy; (b) history of gastric surgery; (c) presence of malignancy, renal failure, or pregnancy; (d) allergy to penicillin and PPIs; and (e) recent use (within the previous 4 weeks) of PPI, bismuth, and antibiotics.

Therapy regimen

All patients received 14-day, high-dose dual therapy comprising rabeprazole (20 mg t.i.d.) and amoxicillin (1 g t.i.d.). The rabeprazole was given half an hour before meals, and amoxicillin was administered after meals. To evaluate *H. pylori* eradication, all patients underwent the HpSA test at least 4 weeks after the completion of the treatment (discontinuation of PPIs and antibiotics). A negative result was defined as successful *H. pylori* eradication.

Statistical analysis

All statistical analysis was performed with the Statistical Packages for the Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA). We performed a per-protocol analysis because a high number of patients dropped out of the study. Categorical variables were calculated as frequencies and percentages and were compared statistically in a chi-square test. Continuous variables were calculated as means±standard deviations. Independent sample *t* tests were performed to assess differences between groups. Two-tailed p lower than 0.05 were considered statistically significant.

RESULTS

This study included 150 patients with H. pylori infection. Of the patients, 96 (64%) were male, and 22 (14.6%) smoked. The rate of successful eradication of *H. pylori* was 91.3% by the high-dose dual therapy. Per-proto-

Table 1. Demographic features of the study population

Demographic variables		Treatment			
		Succeeded (n=137, [91.3%])		Failed (n=13, [8.7%])	
Gender [n (%)]	Female (n=54)	51	(94.4 %)	3	(5.6%)
	Male (n=96)	86	(89.6 %)	10	(10.4%)
			χ^2=1.032	p=0.310	
Smoking status [n (%)]	Smoker (n=22)	20	(90.9%)	2	(9.1%)
	Nonsmoker (n=128)	117	(91.4%)	11	(8.6%)
			χ^2=0.006	p=0.939	
Mean age (years)		39.8±15.6		43.0±13.2	
			t=–0.835	p=0.405	

col rate of success was 94.4% among female patients (n=51) and 89.6% among male patients (n=86); the difference between genders was not significant (p=0.310). The HpSA results were negative at the end of the treatment for 90.9% of patients who smoked (n=20) and 91.4% of those who did not smoke (n=117). Smoking was not found to be a significant factor in eradication rate (p=0.939). The mean age of patients in whom treatment was successful was 39.8±15 years, and that of patients in whom treatment failed was 43.0±13.2 years. We found that age did not make a significant difference in treatment success (p=0.405). Demographic variables are summarized in Table 1. No adverse effects of therapy were observed during the study in any patient. The compliance rate was 96%; 6 patients did not use adequate doses of the treatment protocol, and *H. pylori* was not eradicated in 4 of those patients.

DISCUSSION

In this study, dual therapy consisting of rabeprazole and amoxicillin at high dosages and taken at short intervals eradicated *H. pylori* infection in a high percentage of patients. Compliance with the regimen was high, and no adverse effects of the drugs were observed during treatment. High-dose dual therapy thus appears to be highly effective first-line therapy for *H. pylori* eradication.

Until recently, triple and quadruple therapies that included clarithromycin and metronidazole were recommended as first-line therapies for *H. pylori* infection (3). Unfortunately, the efficacy of these therapies is gradually decreasing worldwide. One of the most important reasons in this decline is the growing resistance to antibiotics. Therapies that include clarithromycin, metronidazole, and levofloxacin have a potential risk of inducing antibiotic resistance because they are commonly used inappropriately as antimicrobial agents. The rates of resistance to clarithromycin, metronidazole, and levofloxacin in our population are 24.8%, 33.7%, and 23.7%, respectively (13). This observation clearly indicates the need for novel regimens that are highly effective against *H. pylori* and to which *H. pylori* has low resistance.

Resistance to amoxicillin, both primary and acquired, is rare in *H. pylori* infections, unlike resistance to clarithromycin or levofloxacin: approximately 0.9% in Turkey and 0.2% to 4% in different regions (9, 13). Amoxicillin is commonly used twice daily in the quadruple or sequential therapies recommended by current guidelines (3). In fact, the efficacy of amoxicillin is closely associated with time and intragastric pH. Because amoxicillin is absorbed rapidly and excreted within 8 hours after administration, the use of amoxicillin more than twice daily can be more effective against *H. pylori* infection by increasing its plasma concentration. The replication rate of *H. pylori* increases in the presence of high intragastric pH; however, because amoxicillin is also more stable and effective when intragastric pH is increased, the bacteria thus become more susceptible to amoxicillin (14).

In addition, amoxicillin and PPIs cannot attain the sufficient plasma concentration in patients with the rapid metabolizer gene *CYP2C19*. Therefore, researchers have tried to increase the effectiveness of the dual treatment by focusing on the dose and frequency of drugs. In a recent study, patients with *H. pylori* received high-dose dual therapy comprising esomeprazole (40 mg t.i.d.) and amoxicillin (1 g t.i.d.) for 10 days; the rate of cure was 87.5% (15). Likewise, we showed the high efficacy of high-dose dual therapy with rabeprazole (20 mg t.i.d.) and amoxicillin (1 g t.i.d.) as first-line therapy, which achieved an eradication rate of 91.3% in this study. In another study, Yang et al. (16) reported that high-dose dual therapy with rabeprazole (20 mg) and amoxicillin (750 mg q.i.d.) over 14 days achieved a cure rate of more than 95% in treatment-naïve patients and was superior to standard regimens as empirical first-line therapy. In Japan, Shirai et al. (17) reported the eradication rate of second-line treatment with rabeprazole (10 mg q.i.d.) and amoxicillin (500 mg q.i.d.) for 14 days was 90.9%.

Because PPIs are potent neutralizers of intragastric pH, we used rabeprazole for acid suppression because of its pharmacological potential features. *CYP2C19* in the liver commonly metabolizes PPIs (18). Rabeprazole is transformed mainly into thioether-rabeprazole via a nonenzymatic pathway and is minimally affected by *CYP2C19* in comparison with other PPIs (19). Rabeprazole has the fewer incidences of drug-drug interactions than other PPIs. It is also a potent acid suppressor with rapid onset of action (20). Twice daily dosing of PPI cannot maintain a pH of more than 4 over a 24-hour period (21). PPIs in more frequent doses (e.g., rabeprazole t.i.d. or q.i.d.) may be effective in maintaining high intragastric pH. All these observations indicate that the effectiveness of dual therapy can be improved by the administration of both drugs at higher doses and frequencies. In fact, high-dose dual therapy for *H. pylori* infection has been investigated and used since 1995 in different populations (11). Researchers initially showed high success rates with the high-dose dual therapy, but controversial results were reported in subsequent studies (22, 23). At the same time, because

the newer triple and quadruple therapies achieved high and constant *H. pylori* cure rates, the researchers have not further investigated dual therapy.

Another reason for the decrease in *H. pylori* eradication rate is poor patient compliance. The Maastricht V consensus report suggested that quadruple concomitant therapies, whether containing or not containing bismuth, should be used in populations with high resistance to clarithromycin, such as the Turkish population. Although these regimens are effective against *H. pylori,* many limitations of these regimens—such as multiple-drug combinations, complicated protocols, and adverse events—lead to low patient adherence in clinical practice. Compliance is crucial for success in *H. pylori* eradication. In a recent study in the Turkish population, Sapmaz et al. (24) reported that compliance with dual therapy was similar with that with quadruple therapy, but quadruple therapy produced a high number of adverse events. A culture-based study showed that adverse events contributed to poor compliance among patients who received quadruple therapy (25). In our study, patients who have received high-dose dual therapy were highly compliant rate, and no adverse effects were reported. Therefore, this treatment regimen seems to be an effective and safe alternative.

Our study has some limitations, as follows: First, we did not use a control or placebo group; therefore, a placebo effect and comparison with other regimens could not be evaluated. Use of a placebo group would have been unethical. We and our colleagues have previously investigated the rates of eradication of *H. pylori* infection by different treatment protocols with the same methods many times (26-28). Therefore, we think that the high-dose dual therapy is effective against *H. pylori* infection in comparison with our previous results. Second, intragastric pH was not measured during the study because of experimental limitations. We thus cannot comment on the relationship between intragastric pH and drug efficacy.

In conclusion, high-dose dual therapy with amoxicillin and rabeprazole was highly effective as a first-line therapy for *H. pylori* eradication. This regimen was also well tolerated and easily available. No adverse effect was observed during the treatment. We think that it could be recommended for the first-line therapy against *H. pylori* infection in areas with high clarithromycin resistance.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gulhane School of Medicine, 23 December 2013/2875.

Informed Consent: Written informed consent was obtained from the patients who participated.

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