

Comparison of 7- and 14-day first-line therapies including levofloxacin in patients with *Helicobacter pylori* positive non-ulcer dyspepsia

Helikobakter pilori pozitif nonülser dispepsili hastalarda birinci basamak tedavide levofloksasin içeren üçlü tedavinin 7 ve 14 günlük etkinliğinin karşılaştırılması

Cemal Nuri ERÇİN, Ahmet UYGUN, Ahmet Burak TOROS, Murat KANTARCIOĞLU, Güldem KİLCİLER, Zülfikar POLAT, Sait BAĞCI

Department of Gastroenterology, Gülhane Military Medical Academy, Ankara

Background/aims: Because of the increasing resistance to clarithromycin and metronidazole, the most frequently used antibiotics in the first-line therapy of *Helicobacter pylori* eradication, new therapeutic alternatives are needed. The aim of this study was to compare the efficacy of 7- and 14-day triple therapy including lansoprazole, levofloxacin and amoxicillin for *Helicobacter pylori* eradication as a first-line therapy. **Methods:** Ninety-one non-ulcer dyspeptic patients infected with *Helicobacter pylori* as diagnosed by both histology and a rapid urease test were included in this study. Patients were randomized to receive either 7- (Group 1; 51 patients) or 14-day (Group 2; 40 patients) therapy with lansoprazole (30 mg b.i.d.), plus levofloxacin (500 mg o.i.d.) and amoxicillin (1000 mg b.i.d.) and they were followed for six weeks. Eradication was assessed by ¹⁴C-urea breath test four weeks after completing the treatment protocols. **Results:** In Group 1, 41 patients completed the treatment and the eradication rate was 34.15%. In group 2, 36 patients completed the treatment and the eradication rate was 72.2% (p= 0.001 vs group 1). **Conclusions:** Triple therapy with lansoprazole, levofloxacin and amoxicillin for 14 days was effective for *Helicobacter pylori* eradication, but 7-day therapy with the same protocol had a lower and unacceptable cure rate and should not be used.

Key words: Levofloxacin, *Helicobacter pylori*, first-line therapy

INTRODUCTION

Helicobacter pylori (*Hp*) infection causes gastritis and gastroduodenal ulcer disease and is also associated with mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. In more than 20 years, researchers dealing with the eradication of this pathogen have been unable to find the ideal protocol, because the generally accepted

Amaç: Birinci basamak *Helikobakter pilori* eradikasyon tedavisinde en sık kullanılan antibiyotikler olan klaritromisin ve metranidazole direncin artması nedeniyle, yeni tedavi alternatiflerine ihtiyaç duyulmaktadır. Bu çalışmanın amacı; birinci basamak eradikasyon tedavisinde lansoprazol, levofloksasin ve amoksisilin'den oluşan üçlü tedavi protokolünün 7 ve 14 günlük etkinliğinin karşılaştırılmasıdır. **Yöntem:** Histoloji ve hızlı üreaz testi ile *Helikobakter pilori* varlığı gösterilmiş nonülser dispepsili 91 hasta çalışmaya alındı. Hastalar 7 günlük (Grup 1: 51 hasta) ve 14 günlük (Grup 2: 40 hasta) lansoprazol 30 mg (2x1), levofloksasin 500 mg (1x1) ve amoksisilin 1000 mg (2x1) tedavisi alacak şekilde randomize edildi ve 6 hafta süre ile izlendi. Eradikasyon, tedavi bitiminden 4 hafta sonra üre nefes testi ile değerlendirildi. **Bulgular:** Grup 1 hastalarının 41'i çalışmayı tamamladı ve eradikasyon oranı %34.15 idi. Grup 2'de ise 38 hasta çalışmayı tamamladı ve eradikasyon oranı %72.22 idi. 7 ve 14 günlük tedaviler arasında eradikasyon oranı açısından anlamlı bir fark tespit edildi (p= 0.001). **Sonuç:** Ondört gün süreyle uygulanan lansoprazol, levofloksasin ve amoksisilinden oluşan üçlü protokol, *Helikobakter pilori* eradikasyonunda etkilidir, ancak 7 günlük tedavide eradikasyon oranı çok düşüktür ve kullanılmamalıdır.

Anahtar kelimeler: Levofloksasin, *Helikobakter pilori*, birinci basamak tedavi

minimum success rate of treatment regimens for *Hp* eradication is 80% (1, 2).

The current standard first-line treatment to eradicate *Hp* is triple therapy, combining a proton pump inhibitor (PPI) with two antibiotics, mainly clarithromycin (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) or metronidazole (500 mg b.i.d.), according

to worldwide guidelines, including the Maastricht III Consensus Report (1-3). The success rate of this treatment varies widely, ranging from 80 to 96% (4-6). Many studies on the efficacy of triple therapy have reported poor results, especially in some Mediterranean regions (7, 8). In fact, cure rates for first-line 14-day triple therapy in our area (Turkey) barely reach 50–60%.

Treatment failure may occur because of inadequate patient compliance or bacterial resistance. The widespread use of macrolide antibiotics for respiratory infections and the subsequent rise in clarithromycin resistance may play a role. According to the literature, clarithromycin resistance reaches 38.5% in Turkey (9). A 10-year epidemiologic analysis (1996-2005) in the Turkish population reported a gradual decrease in eradication success from 80% to 60% with a PPI, amoxicillin and clarithromycin (10).

New treatment options for first-line treatment are currently under investigation. Fluoroquinolones, rifabutin and newer macrolides have been used with variable rates of success (11-13). Levofloxacin is an isomer of ofloxacin with a broad spectrum of activity against several Gram-positive and Gram-negative bacteria and atypical respiratory pathogens (14-16). There have been some studies evaluating the effect of triple therapy including levofloxacin in *HP* eradication as a first-line regimen (17-23).

In this study, our aim was to compare the efficacy of 7- and 14-day triple therapy including lansoprazole, levofloxacin and amoxicillin for *Hp* eradication as a first-line therapy.

MATERIALS AND METHODS

Ninety-one non-ulcer dyspepsia patients with histologically proven *Hp* infection, never treated, were enrolled into this prospective study between November 2007 and April 2008. The study protocol was approved by the local ethical committee of our institute. Informed consent was obtained from each patient before they enrolled in the study. Patients with an active peptic ulcer, previous gastric surgery and malignancy, or allergy to any of the drugs in the first-line treatment were excluded, as well as fertile women who were not using contraceptive precautions.

During the endoscopic examination, four biopsy samples were taken both from the antrum and the corpus at sites at least 2 cm apart. Three biopsy

samples from both the antrum and the corpus were sent for histopathological evaluation and the last samples were put in the same rapid urease test (RUT) slide. The CLO test (Ballard Medical Products, Draper, UT, USA) was used for RUT. A positive result was recorded when the color changed from yellow to pink within 24 hours (h). Hematoxylin–eosin and Toluidine blue preparations of histopathological samples were examined by the pathologists to determine *Hp* status as well as to evaluate gastric mucosa. *Hp* was diagnosed when both histology and the RUT revealed a positive result.

Patients demonstrating a positive histology and positive RUT were randomly separated into two groups to receive treatment as either 7 days (Group 1) or 14 days (Group 2). Treatment protocol was lansoprazole (30 mg b.i.d.), levofloxacin (500 mg o.i.d.) and amoxicillin (1 g b.i.d.) Compliance was questioned and the patients were actively interviewed about side effects. Eradication was measured by ¹⁴C-urea breath test, four weeks after this treatment.

RESULTS

All patients who enrolled in the study had non-ulcer dyspepsia (dyspepsia and gastritis and/or duodenitis at endoscopy) and had positive histology and positive RUT. Seventy-seven patients completed the study. The age and sex distribution of patients in each group who completed the study is shown in Table 1. The two groups were similar with respect to sex and age distribution.

Forty-one patients in Group 1 and 36 patients in Group 2 completed the study. Nine patients in Group 1 and three patients in Group 2 were not available for follow-up, while one patient in each group reported side effects [allergic reaction (from Group 1) and severe nausea/vomiting (from Group 2)] that caused them to stop treatment. Total eradication rate in Group 1 was 34.15% (14/41) and in Group 2 was 72.2% (26/36) (Table 1).

Table 1. Characteristics and eradication rate in patient groups

	Group 1 (n=41)	Group 2 (n=36)	p
Female/Male	31/10	27/9	0.579*
Age (year)	42.36±13.85	42.66±13.27	0.923*
Eradication rate (%)	34.15	72.22	0.001*

Mean ± SD. Chi-Square*, Student's t-test*

Statistics

The distribution characteristics of the variables were evaluated by Kolmogorov-Smirnov test, and then Levene's test was used to determine the homogeneity of variance. The differences between the parameters were measured by chi-square test and independent samples T test where necessary. All values were expressed as mean \pm SD (median). Values of $p < 0.05$ were defined as significant for the analyses.

DISCUSSION

In our study, we found that the eradication rate of patients receiving 7-day triple therapy including lansoprazole, levofloxacin and amoxicillin was 34.15%, whereas this rate was 72.2% in patients receiving the same protocol for 14 days.

Fluoroquinolones have *in vitro* activity against *Hp* (24). A recent *in vitro* study also showed a synergistic effect of quinolone antimicrobial agents and PPIs on strains of *Hp* (25). In this group, levofloxacin has been shown to be an alternative to current standard antibiotics as a means to overcome primary resistance to macrolides and nitroimidazoles (18). Its antibacterial effect is based on the inhibition of bacterial topoisomerase II (26). Levofloxacin is quickly and almost completely absorbed after oral administration with a bioavailability of 100% and a good distribution in tissues and fluids. It has a half-life of 9–16 h with a predominant renal excretion and may be administered in a single daily dose with limited drug interactions and low incidence of side effects (27–29). In our study, one patient in each group was forced to stop treatment because of allergic reaction (in Group 1) and nausea/vomiting (in Group 2).

After the failure of standard first-line treatment, quadruple therapy was recommended as second-line therapy. However, because of the administration of four drugs with a complex scheme and high incidence of adverse effects, levofloxacin was used as a second-line rescue therapy as an alternative. Levofloxacin may retain its activity when *Hp* strains are resistant to clarithromycin and metronidazole (17, 30). These results have been confirmed *in vivo*, indicating that most of the patients with both metronidazole and clarithromycin resistance are cured with the levofloxacin-based regimen (31–33).

In a Spanish study, 10-day rescue therapy with levofloxacin was found to be simple and safe, with an eradication rate of 77% (34). In a meta-analysis

comparing the levofloxacin-based triple therapy with bismuth-based quadruple therapy, it was shown that a 10-day course levofloxacin triple therapy was more effective with higher eradication rates and lower incidence of side effects than 7-day bismuth-based quadruple therapy in the treatment of persistent *Hp* infection (35).

There have been some studies evaluating levofloxacin-based therapy as a first-line therapy. In a 10-day regimen including ranitidine bismuth citrate, levofloxacin and amoxicillin, the eradication rate was found as 88.5% (21). In our study, the eradication rate was 72.2% with the 14-day protocol. This difference may be the result of the additional effect of bismuth in the former study or levofloxacin resistance in our country.

In another study, two 1-week rabeprazole-based triple therapies including levofloxacin were compared. In patients taking rabeprazole, levofloxacin and amoxicillin, the eradication rate was found to be 92%, higher than with the rabeprazole, levofloxacin and tinidazole regimen (18). Nista *et al.* (22) evaluated the eradication rate of patients taking three different protocols. In the first group, taking clarithromycin, amoxicillin and esomeprazole, the eradication rate was 75%; in the second group, taking clarithromycin, metronidazole and esomeprazole, the rate was 72%; and in the third group, taking clarithromycin, levofloxacin and esomeprazole, the rate was 87%. They concluded that 7-day levofloxacin-based triple therapy can achieve higher eradication rates than standard regimens, and that this protocol can be the most effective in first-line anti-*Hp* therapy. In a 7-day triple therapy with esomeprazole, levofloxacin and clarithromycin, Schrauwen *et al.* (23) found the eradication rate as 93%. If we evaluate this protocol for our country, it is impossible to use because we are trying to overcome the clarithromycin resistance by adding levofloxacin in the first-line therapy. Giving levofloxacin and clarithromycin together in the same protocol is not suitable for our country with its high clarithromycin resistance.

In a study from Turkey, the authors compared the classic triple therapy with a protocol including lansoprazole, amoxicillin and levofloxacin, and did not find any difference regarding the eradication rate. They concluded that levofloxacin-based triple therapy is an alternative eradication protocol but it has no therapeutic benefit (36).

The most important problem in levofloxacin-based

regimens is resistance. Resistance to quinolones is easily acquired and broad consumption of quinolones will increase the resistance rates (20, 37, 38). Perna et al. (39) showed that in the presence of levofloxacin resistance, the efficacy and also the eradication rate of levofloxacin-based regimens were decreasing. In light of these data, it was proposed that these drugs should be used as initial therapy only in areas where primary resistance is low (e.g. <10%) or only after susceptibility test (40).

As an alternative to all these eradication protocols, in a sequential therapy using esomeprazole-amoxicillin followed by gatifloxacin (a fluoroquinolone), the eradication rate was found as 80%, and the authors drew attention to the pre-treatment susceptibility testing for the fluoroquinolone resistance (41).

A major drawback of the present study is the lack of pre-treatment susceptibility testing to levofloxacin and the small number of patients in the study groups.

In conclusion, in light of the data about the generally accepted minimum success rate of treatment regimens for *Hp* eradication as 80%, the eradication rate in the present study with levofloxacin-based first-line triple therapy was found to be lower with 7-day treatment, but may be acceptable and considered an alternative treatment with 14 days. If there is another protocol, with an eradication rate above 80%, it would be beneficial to use it, especially in Turkey. Further studies are needed with larger patient populations and a susceptibility component.

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