ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Assessment of *Helicobacter pylori* eradication rate of triple combination therapy containing levofloxacin

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Background/aims: *Owing to its high efficacy, ease of use, perfect adaptation and low complication profile, it is suggested that the triple therapy combination consisting of levofloxacin, amoxicillin and proton pump inhibitor may be an alternative for the first-line and second-line treatment of Helicobacter pylori. The aim of this study is to evaluate the efficacy of the triple therapy regimen containing two different doses of levofloxacin in the first-line eradication treatment.* ***Material and Methods:*** *110 naïve patients with anti Helicobacter pylori treatment indications according to Maastricht III Consensus Report were included to the study. Patients were randomized into two groups as the patients treated with a levofloxacin (500 mg o.i.d), amoxicillin (1 g b.i.d) and proton pump inhibitor (b.i.d) combination for 10 days (Group 1, n=60) and patients treated with a levofloxacin (500 mg b.i.d), amoxicillin (1 g b.i.d) and proton pump inhibitor (b.i.d) combination for 10 days (Group 2, n=50). Eradication rate was assessed at the 6th week of therapy just subsequent to termination of treatment.* ***Results:*** *110 treatment-naïve patients (60 female, mean age: 44.1±14.7 years) were randomized and all patients completed the study. Helicobacter pylori eradication of the Group 1 was 60% and in Group 2 was 72.7%. The difference between the two groups was not statistically significant (p=0.427). None of patients experienced severe complication that would lead to discontinuation of therapy.* ***Conclusion:*** *It is observed that the efficacy of the triple therapy combination containing levofloxacin is not within acceptable limits for the first-line Helicobacter pylori eradication.*

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

Helikobakter pilori eradikasyonunda levofloksasin içeren üçlü kombinasyon tedavisi

Amaç: *Yüksek etkinlik, kullanım kolaylığı, mükemmel uyum ve düşük yan etki profili nedeniyle levofloksasin, amoksisilin ve proton pompa inhibitörü içeren üçlü tedavi kombinasyonunun Helikobakter pilori birinci ve ikinci basamak tedavisinde alternatif bir seçenek olabileceği ileri sürülmektedir. Bu çalışmada amaç, birinci basamak eradikasyon tedavisinde, iki farklı dozda levofloksasin içeren üçlü tedavi rejiminin etkinliğini değerlendirmektir.* ***Yöntem ve Gereç:*** *Maastricht III Konsensus Raporu'na göre anti Helikobakter pilori tedavi endikasyonu olan naif 110 hasta çalışmaya alındı. Helikobakter pilori pozitifliği histoloji, hızlı üreaz testi ve kültür testlerinden en az ikisi ile gösterildi. Hastalar levofloksasin (1x500 mg), amoksisilin (2x1 g) ve proton pompa inhibitörü (2x1) kombinasyonu ile 10 gün (Grup 1, n=60) ya da levofloksasin (2x500 mg), amoksisilin (2x1 g) ve proton pompa inhibitörü (2x1) kombinasyonu ile 10 gün (Grup 2, n=50) süreyle tedavi edilenler olmak üzere iki gruba randomize edildi. Eradikasyon başarısı tedavi bitiminden en erken 6 hafta sonra değerlendirildi ve üç yöntemin tümünde de Helikobakter pilori negatifliği olarak kabul edildi.* ***Bulgular:*** *110 naif hasta (60 K, 50 E, yaş ortalaması; 44.1±14.7) randomize edildi, hastaların tümü çalışmayı tamamladı. Grupların yaş ve cinsiyet ortalamaları benzerdi. Helikobakter pilori eradikasyonu Grup 1'de %60, Grup 2'de ise %72.7 idi ve gruplar arasında fark anlamlı değildi p=0.427). Hiçbir hastada tedavinin erken kesilmesini gerektirecek ciddi yan etki görülmedi. Sadece 5 hastada (%4.5) hafif yan etkiler görüldü. Peptik ülser hastalığı olanlar ve nonülser dispepsisi olan hastalar arasında eradikasyon başarısı arasında fark görülmedi.* ***Sonuç:*** *Levofloksasin içeren üçlü tedavi rejiminin birinci basamak Helikobakter pilori eradikasyonunda etkinliğinin kabul edilebilir sınırlarda olmadığı görüldü.*

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

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Manuscript received: 12.12.2010 **Accepted:** 05.02.2011

Turk J Gastroenterol 2011; 22 (6): 582-586
doi: 10.4318/tjg.2011.0255

This study was presented at the 26th National Gastroenterology Week, October 14-18 2009, Ankara
Turk J Gastroenterol, 2009;20(Sup 1):23, S-43.

INTRODUCTION

As it is one of the most common infectious diseases closely related with duodenal or gastric ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma, eradication of *Helicobacter pylori (H. pylori)* maintains its importance. Despite the performance of various treatment regimens, the ideal treatment is still under debate. In the first Maastricht Consensus Conference (1997) report, it was recommended that the treatment regimen must achieve a minimum 80% intention to treat (ITT) eradication rates (1). Furthermore, the consensus reports also recommend triple therapies consisting of proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole combination for the first-line treatment (2-4). However, it has been reported that the eradication rates before 2000, which were over 90% (5,6), achieved with the administration of the triple standard therapy, have declined to 70% in the 2000's (7,8). The main reasons for the insufficiency of these regimens are non-compatibility of the patients and gradually increasing antibiotic resistance (clarithromycin and metronidazole resistance).

Recently, it has been reported that the triple therapy regimen consisting of levofloxacin, amoxicillin and PPI enables the eradication in ratios over 80% both in the first-line and second-line treatments, and it has been suggested that this regimen can be used as an alternative to the standard triple therapy (9-11). Romano et al. (12) concluded that levofloxacin-containing therapy is more effective, equally safe and cost-saving compared to a clarithromycin-containing therapy. According to some other recent studies, ranitidine bismuth citrate and levofloxacin-based therapies were shown to obtain the same eradication rates as standard triple regimens (13).

The goal of this study was to examine the efficacy of the triple therapy regimen containing different doses of levofloxacin in our country, in which both *H. pylori* prevalence and clarithromycin resistance are high.

MATERIALS AND METHODS

Patients

The study was designed as a prospective, open label and single-center study and was carried out at Ankara University, Faculty of Medicine, Gastroenterology Clinic between September 2008 and 2009. One hundred and ten naive patients who were diagnosed as *H. pylori*-positive by gastroscopic examination administered upon the patients' dyspeptic complaints were included in the study.

Exclusion Criteria

Patients who were receiving H_2 receptor antagonists, PPI, compounds containing bismuth, nonsteroidal anti-inflammatory medications or antibiotics, had accompanying serious comorbid conditions or received *H. pylori* eradication treatment previously were excluded.

H. pylori Diagnosis and Eradication Assessment

Peptic ulcer and non-ulcer dyspepsia were the diagnosed pathologies on endoscopic examination. Two samples were obtained by endoscopic biopsy from the corpus and antrum. *H. pylori* positivity was confirmed by two positive rapid urease tests, histopathologic examination and microbiologic culture. The earliest tests to confirm *H. pylori* eradication were performed at the 6th week. Eradication was confirmed by negative histological analyses, rapid urease tests and microbiologic culture.

Treatment Protocols

Patients were treated with either levofloxacin (500 mg o.i.d.) (Group 1) or levofloxacin (500 mg b.i.d.) (Group 2), both combined with amoxicillin (1 g b.i.d.) and PPI (b.i.d.) for 10 days.

Statistical Analysis

Data was evaluated by the Statistical Package for the Social Sciences (SPSS) 16.0 computer program. Statistical analyses were carried out by T tests and chi-square tests. P values less than 0.05 were significant.

RESULTS

One hundred and ten naive patients were enrolled in the study. Sixty patients were treated with 500 mg (o.i.d.) levofloxacin and the remaining 50 patients were treated with 500 mg (b.i.d.) levofloxacin, both also consisting of amoxicillin (1 g b.i.d.) and PPI (b.i.d.) combination and lasting for 10 days. No significant difference was observed between the two groups according to mean age and gender distribution.

Incidences of peptic ulcer and non-ulcer dyspepsia were 8% and 92%, respectively. Mild complications such as nausea (4 patients), indigestion (3 patients) and diarrhea (1 patient) were observed in

4.5% of patients. None of our patients experienced a serious complication that would lead to discontinuation of the therapy. No significant difference was present between the two groups in terms of peptic ulcer and related complications. All 110 patients completed the study.

Eradication rates were 60% and 72.7% in Groups 1 and 2, respectively, and the difference was non-significant (60.0% vs 72.7%, p=0.427) (Table 1). Eradication rates were similar in the patients with peptic ulcer and non-ulcer dyspepsia.

DISCUSSION

Since 1990, standard triple therapy was determined as the classical regimen in the eradication of *H. pylori* (2-4). Eradication rates of first-line standard therapy reduced from 90% to less than 70-80% (5-8,14-16). Especially resistance to clarithromycin plays a crucial role in the development of inadequate eradication rates and decreases the eradication rates to as low as 70% (17). The resistance rates vary globally and have increased in the last decade when compared to studies from Europe carried out before 1997. In a French study, clarithromycin resistance rates were 19.2% and 26% in native patients and the entire population, respectively (18). The resistance rates were 3.9% prior to 1997 and 9.3% in recent years (19). Onder et al. (20) stated that clarithromycin resistance rates were 48.2% in Turkey. Primary and secondary resistance rates were determined as 16.45% and 27.2% by Tuzun et al. (21).

Eradication rates of standard triple therapy decreased subsequent to increased clarithromycin resistance rates. A national meta-analysis performed on 94 studies comprising standard triple therapy combinations revealed that from 1996 to 2005, the eradication rates were reported as 79.4%, 83.7%, 81.8%, 81.8%, 75.1%, 61.3%, 65.6%, 65.1%, 55.3%, and 61.1%, respectively, and after 2000, a significant decrease in the eradication rates was noted (22). A retrospective analysis carried out in our clinic demonstrates that the eradication rates achieved with standard triple therapy combinations between 2004 and 2008 were 66.2%, 75.4%, 71.5%, 72%, and 73.4%, respectively (23). However, when these ratios were compared with the results of two studies performed in our clinic before 2000, it was shown that after 2000, the eradication rates decreased significantly with the standard triple therapy. In one of these studies, which was performed from 1995-1997, the standard triple therapy that was administered for 1 week or 2 weeks was compared with ranitidine, bismuth substrate, clarithromycin, and amoxicillin combination (24). In that study, the eradication rates were reported as 72%, 90% and 91%, respectively. No differences could be demonstrated between the standard triple therapy, which was applied for 2 weeks, and triple combination with bismuth; however, both treatment regimens were claimed to be more effective than the 1- week standard triple combination therapy. In the other study, comparisons of short- and long-term lansoprazole, clarithromycin and amoxicillin combinations containing either 750 mg or 1000 mg clarithromycin doses were made (25). In the group treated with lansoprazole (30 mg o.i.d. for 4 weeks), clarithromycin (750 mg o.i.d. for 2 weeks) and amoxicillin (1 g b.i.d. for 2 weeks) combination, the eradication rate was 100%, and in the group treated with lansoprazole (30 mg o.i.d. for 2 weeks), clarithromycin (500 mg b.i.d. for 2 weeks) and amoxicillin (1 g b.i.d. for 2 weeks) combination, the eradication rate was 95%; however, no statistical differences between the groups could be demonstrated. Furthermore, it was argued that in terms of the eradication rates, there were no differences between the treatment periods, PPI types and treatment indications.

Table 1. Demographic features of the patients included in the study and eradication rates

	Group 1 (10 days) Levofloxacin (500 mg o.i.d.) Amoxicillin (1 g b.i.d.) PPI (b.i.d.)	Group 2 (10 days) Levofloxacin (500 mg b.i.d.) Amoxicillin (1 g b.i.d.) PPI (b.i.d.)	P value
Patient (n, %)	60 (54.5%)	50 (45.5%)	
Age (mean±SD)	43.9±15.3	45.1±12.0	0.802
Gender (M/F)	24/36	26/24	0.373
Adverse effect	4.5%	4.7%	0.346
Eradication ratio	36 (60%)	36 (72.7%)	0.427

Levofloxacin is an antibiotic of the fluoroquinolones group that is demonstrated to be considerably effective against *H. pylori* in in vitro studies; primary resistance against levofloxacin is not observed very frequently and it has a synergic effect together with PPI (10,26,27). However, in the regions where these medicines are prevalently used, quinolone resistance develops easily, and today, quinolone resistance is reported to be relatively high. The triple therapy regimen containing levofloxacin is recommended as the first alternative in *H. pylori* eradication without application of any primary sensitivity tests in the regions where primary resistance against levofloxacin is approximately 10% (28). In the regions where primary resistance is higher, treatment is recommended to be performed after the application of the antibiotic sensitivity tests.

In the recent studies performed on the treatment regimens containing levofloxacin, it has been demonstrated that levofloxacin is effective in the first- and second-line treatments, and with an efficacy rate over 80%, it can be included in the standard triple therapy instead of clarithromycin in the first-line eradication therapy of *H. pylori* (9-11,29,30). It has also been suggested that 7 days levofloxacin (500 mg b.i.d.), amoxicillin (1 g b.i.d.) and esomeprazole (b.i.d.) combination is more effective in the fist-line treatment than the triple treatment containing clarithromycin (92.9% vs 83.9%); levofloxacin may also be effective in clarithromycin- and metronidazole-resistant *H. pylori* strains (10). Levofloxacin-based and sequential therapy is superior to the standard triple scheme as a first-line regimen in a setting with high clarithromycin resistance (31).

In another study comparing the efficacy of levofloxacin (500 mg o.i.d.) and rabeprazole combined with either amoxicillin (1 g b.i.d.) or tinidazole (500 mg o.i.d.), success rates were 92% and 90%, respectively, and these combinations were recommended as alternatives to clarithromycin (9).

In a recent study carried out by Ercin et al. (32), the efficacy of 7- and 14-day triple therapy consisting of lansoprazole, levofloxacin and amoxicillin as a first-line therapy was compared. 14-day triple therapy was significantly more effective than 7-day triple therapy. Results of the study indicate that this regimen could be an alternative to classical therapy.

In a study carried out to determine the proper dosage and treatment sessions of levofloxacin- containing regimens, it was pointed out that the levofloxacin dose had no significant effect on the eradication rate (77.5% with both 500 mg o.i.d. and 500 mg b.i.d. doses); however, the duration of therapy significantly affects the eradication rate (10-day therapy had higher success rate (85%) and lower complication rates than 7-day therapy) (33). It has been demonstrated that the triple regimen that combines levofloxacin with clarithromycin for 7 days was more effective than clarithromycin, esomeprazole and amoxicillin or metronidazole combination (87% vs 75%, $p<0.05$; 87% vs 72%, $p<0.01$), and it has also been reported that this combination was more effective in the first-line therapy (11).

Nevertheless, in a study from Spain carried out in 2009, the success rate of the triple treatment containing levofloxacin in the first-line therapy was 71.8% in ITT analysis and 74.6% in per protocol analysis (PPA), and no difference was found between this regimen and classical triple therapy. It was also stated that triple therapy with a PPI, amoxicillin and levofloxacin for 10 days is a well-tolerated treatment that is easy to comply with; however, it has low efficiency -less than 80%- and is not recommended as a first-choice treatment for *H. pylori* eradication (34).

Eradication rates of levofloxacin in two different doses (500 mg o.i.d. vs b.i.d.) combined with amoxicillin and PPI for 10 days were 60% and 72.7%, respectively, in our study.

Chen et al. (35) emphasized that efficacy and tolerability of once-daily and twice-daily triple therapy (levofloxacin 500 mg, esomeprazole 40 mg and clarithromycin 500 mg) were equal; however, none of the regimens was effective enough to be considered as a recommendable first-line treatment.

In conclusion, despite its low complication profile and availability, levofloxacin-amoxicillin-PPI combination is an unsuitable alternative to clarithromycin-amoxicillin-PPI combination, at least in the Turkish population, due to the lower eradication rate. It is essential to determine the incidence of fluoroquinolones resistance of *H. pylori* in the Turkish population and to develop alternative therapeutic regimens.

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