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Can lansoprazole, amoxicillin, and clarithromycin combination still be used as a first-line therapy for eradication of *helicobacter pylori*?

Lansoprazol, amoksisilin ve klaritromisin kombinasyonu *H. pylori* eradikasyonunda hala ilk basamak tedavi olarak kullanılabilir mi?

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Background/aims: *To determine H. pylori eradication rate with lansoprazole-amoxicillin-clarithromycin treatment regimen, which is the most frequently used as first-line therapy, in the Kırıkkale region.* ***Methods:*** *One hundred and five patients (44 male, 61 female) with H. pylori infection were included in the study. Patients were divided into two groups based on the endoscopic findings: non-ulcer dyspepsia (n=84, 31 male, 53 female) and acute gastric or duodenal ulcer (n=21, 13 male, 8 female) groups. The diagnosis of H. pylori infection was confirmed if both the urease test and histological examination, which were performed on endoscopic biopsies, were positive. Lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg were given twice daily for 14 days to all patients. Endoscopic biopsies were repeated for the evaluation of eradication three months after the treatment.* ***Results:*** *Ninety-six patients completed the study. Eradication rates were found to be 45.8% (44 of 96) in all patients, 42.1% (32 of 76 patients) in the non-ulcer dyspepsia group and 60% (12 of 20 patients) in the gastric or duodenal ulcer group for per protocol analysis, and the difference between non-ulcer dyspepsia and gastric or duodenal ulcer groups was not statistically significant (p=0.208).* ***Conclusions:*** *Lansoprazole-amoxicillin-clarithromycin treatment regimen, the most frequently preferred regimen in H. pylori eradication, is ineffective in our region. The low eradication rates observed with lansoprazole-amoxicillin-clarithromycin, at least in our region, bring into question its use as a first-line therapy. The use of alternative treatment protocols or antibiotic susceptibility test before the treatment may be helpful in achieving successful eradication with first-line therapy.*

Key words: *Helicobacter pylori* eradication, lansoprazole, amoxicillin, clarithromycin

Amaç: *H. pylori eradikasyonunda en sık kullanılan tedavi rejimi olan lansoprazol-amoksisilin-klaritromisin ile Kırıkkale bölgesinde eradikasyon oranını belirlemek.* ***Yöntem:*** *H. pylori infeksiyonu tanısı konulan 105 hasta (44 erkek, 61 kadın) çalışmaya alındı. Endoskopik bulgulara göre hastalar iki gruba ayrıldı: Non-ülser dispepsi (n=84, 31 erkek, 53 kadın) ve akut gastrik veya duodenal ülser (n=21, 13 erkek, 8 kadın) grupları. H. pylori infeksiyon tanısı endoskopik biyopsilerde yapılan üreaz testi ve histolojik incelemenin her ikisinin de pozitif olması ile konuldu. Tüm hastalara lansoprazol 30 mg, amoksisilin 1 g ve klaritromisin 500 mg günde iki kez 14 gün boyunca verildi. Eradikasyonun değerlendirilmesi için tedaviden üç ay sonra endoskopik biyopsiler tekrarlandı.* ***Bulgular:*** *Çalışmayı 96 hasta tamamladı. Per protokol analizde eradikasyon oranı tüm hastalarda %45,8 (44/96), NUD grubunda %42,1 (32/76), GDU grubunda ise %60 (12/20) olarak bulundu ve NUD ve GDU grupları arasındaki fark istatiksel olarak anlamlı değildi (p=0.208).* ***Sonuç:*** *Sonuç olarak H. Pylori tedavisinde en sık kullanılan tedavi protokolü olan lansoprazol-amoksisilin-klaritromisin protokolü bölgemizde başarısız bulunmuştur. Düşük eradikasyon oranları, en azından bizim bölgemizde, lansoprazol-amoksisilin-klaritromisin rejiminin ilk basamak tedavide kullanılabilirliğini sorgular hale gelmiştir. Alternatif tedavi protokollerinin kullanılması veya tedavi öncesi antibiyotik duyarlılık testi yapılması ilk basamak tedavide başarılı eradikasyon elde etmek için yararlı olabilir.*

Anahtar kelimeler: *Helicobacter pylori* eradikasyonu, lansoprazol, amoksisilin, klaritromisin

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is strongly associated with gastroduodenal diseases such as chronic active gastritis, peptic ulcer disease and gastric malignancies (1, 2, 3). Different treatment regimens for eradication of *H. pylori* have been widely used, but none of them have an optimal eradication rate. Recently, in the Maastricht 2-2000 Consensus Report, drug combinations consisting of proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) plus clarithromycin plus amoxicillin or metronidazole for 7-14 days were proposed as the first-line therapy for eradication of *H. pylori* (4). Combination therapies including PPIs are preferred, especially for patients with ulcer, as

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they provide rapid symptomatic improvement and endoscopic healing as well as having a bacteriostatic effect on *H. pylori* (5-7). Clarithromycin, a macrolide antibiotic, has an antimicrobial spectrum similar to that of erythromycin, but it is better absorbed, has better acid stability and tissue penetration and is concentrated in mucosa and mucus layer. In humans, clarithromycin is metabolized to its chief metabolite, 14-OH clarithromycin, which is two times more active, and its MIC value decreases 10-fold with increasing pH (8, 9). Amoxicillin is frequently preferred in *H. pylori* eradication since almost no resistance develops (10, 11). Because of the mentioned advantages and relatively lower rate of adverse effects in comparison with the regimens containing metronidazole or bismuth, PPI-amoxicillin-clarithromycin combination regimen is the most frequently preferred in our country as well as throughout the world (4).

In Turkey, the eradication rate of lansoprazole, amoxicillin and clarithromycin (LAC) combination therapy for 14 days has been reported to be between 44% and 74% in some recent studies (12, 13). The low eradication rates with LAC treatment observed in our country bring into question its role as the first-line treatment for *H. pylori* eradication, since any treatment regimen used should provide an eradication rate of at least 80% (4). In the present study, we aimed to determine the *H. pylori* eradication rate with the LAC regimen, which is the most frequently preferred for first-line therapy, in the Kırıkkale region.

MATERIALS AND METHODS

Between November 2002 and March 2004, 105 patients (44 male, 61 female) who underwent upper gastrointestinal endoscopy at Kırıkkale University Hospital because of dyspeptic complaints and with *H. pylori* infection were included in the study. Patients were divided as non-ulcer dyspepsia (NUD) and acute gastric or duodenal ulcer groups (GDU) according to endoscopic findings. There were 84 patients (31 male and 53 female) in the NUD group and 21 patients (13 male and 8 female) in the GDU group. Demographic features of the patients are shown in (Table 1).

For the detection of *H. pylori*, two endoscopic biopsy specimens (one from antrum and one from corpus) for the rapid urease test (CLO test, Balard, USA) and four specimens (2 from antrum within 2 to 3 cm from pylorus, 2 from corpus) for histopathologic examination were taken. Biopsy specimens were stained with hematoxylin-eosin and assessed for the presence of *H. pylori*. The diagnosis of *H. pylori* infection was confirmed if both the urease test and histology were positive.

Table 1. Demographic features of the patients with non-ulcer dyspepsia (NUD) and patients with gastric or duodenal ulcer (GDU)

	NUD (n=84)	GDU (n=21)	Total (n=105)	p*
Age (year, mean±SD)	40.9±11.2	40.0±11.6	40.7±11.3	NS
Gender (male/female)	31/53	13/8	44/61	<0.05
Smoking n (%)	26 (30.9)	11 (52.4)	37 (35.2)	NS
Alcohol intake n (%)	4 (4.8)	2 (9.5)	6 (5.7)	NS

NS: Not significant
*Statistical significance between NUD and GDU groups

Patients were excluded if they had received *H. pylori* eradication therapy, H_2 receptor antagonist or PPI within the last four weeks or nonsteroidal antiinflammatory drugs (NSAIDs) within the last two weeks prior to the study. Patients with hypersensitivity against any of the drugs used in this study, pregnancy or lactation, liver or renal failure, severe systemic diseases (e.g. diabetes mellitus, hyper- or hypothyroidism, etc.), absorption or motility disorders and past history of gastric or intestinal surgery were also excluded. Lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg were given twice daily for 14 days to all patients. Patients were informed about the possible side effects of the treatment and were asked to keep a record in regard to those side effects. Adequate compliance was defined as an intake of greater than 80% of each drug, as determined by interview and tablet count following the treatment phase of the study. After the eradication treatment, the patients were only allowed to use antacids on demand until two weeks before control examination. Endoscopy was repeated and biopsies were taken in the same manner as with the initial biopsies three months after the treatment for the evaluation of eradication. Successful eradication was defined if both urease test and histopathological examination were negative for *H. pylori*. The eradication rates were calculated on intention-to-treat (ITT) and per protocol (PP) basis. The study protocol conformed to the Helsinki Declaration. Informed written consent was obtained from all patients.

Statistical analysis

Statistical analysis was performed with chi-square and Student's t tests using the SPSS for Windows (version 10.01; SPSS, Inc., Chicago, Illinois,

USA). Statistical significance was assumed to be $p<0.05$.

RESULTS

Ninety-six (91.4%) patients (41 males, 55 females; mean age: 40.1±11.2 yr, range: 18-71 yr) completed the study protocol. Two female patients in the NUD group could not complete the treatment protocol because of drug adverse effects and seven patients [6 NUD (2 male, 4 female) and 1 GDU (male)] were further excluded from the study since they refused the control endoscopy. Eradication rates were found to be 41.9% (44 of 105 patients) for ITT and 45.8% (44 of 96 patients) for PP analysis in all patients. Additionally, eradication rates were found to be 38.1% (32 of 84 patients) for ITT and 42.1% (32 of 76 patients) for PP analysis in the NUD group, and 57.1% (12 of 21 patients) for ITT and 60% (12 of 20 patients) for PP analysis in the GDU group. Eradication rates for ITT and PP analysis were similar between NUD and GDU groups (p=0.208).

Twenty-one of 105 patients (20%) experienced one or more drug adverse effects (Table 2). Treatment was stopped in two patients because of diarrhea occurring on the second day of the treatment in one and epigastric pain and nausea experienced on the fourth day of the treatment in the other; however, adverse effects did not require cessation of the treatment in 19 patients. Control endoscopy revealed complete healing of ulcers in all patients in the GDU group.

Table 2. Drug adverse effects observed in the study population on eradication treatment of *H. pylori*

Adverse effect	NUD (N=84) n (%)	GDU(N=21) n(%)	Total (N=105) n (%)
Nausea	2 (2.4)	0	2 (1.9)
Epigastric pain	3 (3.6)	1 (4.8)	4 (3.8)
Diarrhea	1 (1.2)	0	1 (1)
Headache	3 (3.6)	0	3 (2.9)
Taste disturbances	7 (8.3)	1 (4.8)	8 (7.6)
Fatigue	4 (4.8)	1 (4.8)	5 (4.8)
Loose defecation	5 (5.9)	1 (4.8)	6 (5.7)

Note: Some patients experienced more than one adverse effect
NUD: Non-ulcer dyspepsia; GDU: Gastric or duodenal ulcer

DISCUSSION

The discovery of *H. pylori* (14) has been considered a revolution in gastroenterology since the treatment strategies of some gastroduodenal diseases have changed. In the present study, the eradication rate with LAC treatment for 14 days was found to be 45.8% in the Kırıkkale region. This rate is lower than the rates that have been reported from developed countries and also lower than rates reported previously from this country, but it is consistent with the rates reported recently from various regions of our country.

Clarithromycin is currently accepted as the most effective drug in *H. pylori* infection, with a 42% eradication rate (5, 8, 15). Moreover, the eradication rate is increased with the use of additional antibiotics (16), and combinations including PPIs have become a current issue of interest, with the demonstration of the bacteriostatic effect of PPIs (6, 7). In 1997, the European *Helicobacter Pylori* Group recommended the PPI-amoxicillin-clarithromycin triple regimen for seven days as the first-step eradication therapy (17). At that time, the eradication rates in western countries were reported as 86% (18) with this regimen for seven days and as 78-95% for 14 days (18, 19, 20). The results from Turkey were also similar, with 87-98% eradication rates (21, 22, 23).

However, in recent years, low eradication rates (between 65%-86%) with PPI-based triple regimen (PPI plus amoxicillin plus clarithromycin) have been reported from several European countries (24, 25) (Table 3). They postulated that the main causes of the low eradication rate might be antibiotic resistance, inconsistency with therapy and early cessation of treatment due to adverse effects of the drugs used.

A significant reduction in the eradication rate was also observed in our country in recent years (26-31). Eradication rates were reported between 43.5%-83% with LAC for 14 days (26-30) and about 40% with OAC for 14 days (29, 31) (Table 3). Our eradication rate (45.8%) was also consistent with those rates reported from Turkey in recent years. Although the eradication rates have been reported to be similar with 7- and 14-day treatment regimens in developed countries, 7-day treatment regimens are not recommended in developing countries because of low eradication rates reported from these countries using these regimens (4, 5).

It has been proposed that the main cause of reduction in eradication rates with LAC is the gradual increase in clarithromycin resistance (25, 32). Vakil et al. (32) from the U.S. found the primary clarithromycin resistance as 4% between 1993-1994

Table 3. *Helicobacter pylori* eradication rates reported with different proton-pump inhibitor-based triple regimens

Authors	Country-year	Regimen	Duration	Eradication rate (%)
Rinaldi et al. (24)	Italy-1999	OAC	7 days	86%
		LAC	7 days	75%
		PAC	7 days	78%
Lamouliatte et al.(25)	France-2000	OAC, LAC or PAC	7 days	65%
Şimşek et al. (26)	Turkey-2000	LAC	7 days	76%
		LAC	14 days	83%
Özaslan et al. (27)	Turkey-2001	LAC	14 days	69%
Erçin et al. (28)	Turkey-2002	LAC	14 days	72%
Sezgin et al. (29)	Turkey-2002	LAC	14 days	43.5%
		OAC	14 days	40.8%
Alkım et al. (30)	Turkey-2003	LAC	14 days	67%
Gümürdülü (31)	Turkey-2003	OAC	14 days	40.7%

OAC: omeprazole-amoxicillin-clarithromycin; LAC: lansoprazole-amoxicillin-clarithromycin; PAC: pantoprazole-amoxicillin-clarithromycin

and as 12.6% between 1995-1996, and secondary clarithromycin resistance as 25%. Crone et al. (33) in their study of children in Austria found the primary clarithromycin resistance as 14% in 1997 and as 28% in 2000, and they proposed that common use of clarithromycin in children should be restricted to better-defined indications, otherwise resistance of *H. pylori* to clarithromycin may also become a problem in the treatment of adults. In 2001, Tankovic et al. (34) from France found primary clarithromycin resistance as 19% and secondary resistance as 69%. Cabrita et al. (35) from Portugal reported that primary clarithromycin resistance rose from 4.6% to 14.6% in a decade between 1990-1999, and that no resistance to amoxicillin and tetracycline was observed. Wolle et al. (36) from Germany found total primary clarithromycin resistance as 2.2% between 1995-2000, and reported that there was no increase in primary clarithromycin resistance throughout this period and that no resistance was observed to amoxicillin and tetracycline. It was shown that clarithromycin resistance develops due to a point mutation in the 23S rRNA gene, a result of which is impairment in the binding of antibiotic to ribosome (37). In recent years, bismuth compounds were reported to decrease the development of resistance to antibiotics (38).

There are studies indicating that clarithromycin resistance has been on the increase in our country in recent years. Palabıyıkoğlu et al. (39) in 1997 found primary clarithromycin resistance as 0% and secondary resistance as 3.2%, and observed that no primary or secondary resistance to amoxicillin developed. Kantarçeken et al. (40) in 2000 in their study on 51 patients found primary clarithromycin resistance as 9.8%, and tetracycline resistance as 3.9%, but no resistance to amoxicillin. Engin et al. (41) in 2001 found primary clarithromycin resistance as 11.4%, but no resistance to amoxicillin and tetracycline. Çırak et al. (42) in 2003 reported primary clarithromycin resistance, with the demonstration of 23S rRNA as gene point mutation by PCR technology, as 16.2%. Işıksal et al. (43) detected clarithromycin resistance with E-test method as 18%.

In conclusion, LAC treatment regimen, the most popular *H. pylori* eradication regimen, is ineffective in our region. Low eradication rates with LAC, at least in our region, bring into question its use as a first-step therapy. Alternative treatment protocols or antibiotic susceptibility test before the treatment may be helpful in achieving successful eradication with first-line therapy.

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