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Recent success of pantoprazole -or lansoprazole- based clarithromycin plus amoxicillin treatment in the eradication of *Helicobacter pylori*

Pantoprazol veya lansoprazol ile amoksisilin ve klaritromisin içeren rejimlerin *Helikobakter pilori* eradikasyonundaki güncel durumu

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Background!aims: *There are some reports showing that resistance of Helicobacter pylori (H. pylori) to clarithromycin has increased in recent years. We aimed to investigate the current success of a most popular first-line eradication regimen by using two different proton pump inhibitors: lansoprazole and pantoprazole.* ***Methods:*** *Ninety patients with H. pylori-positive functional dyspepsia were randomized to receive pantoprazole 40 mg b.i.d. or lansoprazole 30 mg b.i.d. in addition to amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 14 days in a multicenter study. H. pylori infection was determined by histological examination and a rapid urease test. A follow-up endoscopy was performed to assess the H. pylori eradication six weeks after the end of therapy.* ***Results:*** *Seventy-nine patients completed the study protocol properly. The H. pylori eradication rates according to per protocol analysis were 70% in group pantoprazole, amoxicillin and clarithromycin (28/40) and 69.2% in group pantoprazole, amoxicillin and clarithromycin (27/39). The eradication rates according to intention to treat analysis were 62.2% and 60% in lansoprazole, amoxicillin, clarithromycin, pantoprazole, amoxicillin, clarithromycin groups, respectively. The eradication rates were similar in both protocols (p>0.05).* ***Conclusions:*** *The most popular first-line eradication protocols of H. pylori achieved only a moderate success in the current study. Alternative therapy options are needed instead of clarithromycin-based triple treatment for eradication of H. pylori. The choice of proton pump inhibitor is not important in the eradication rate of H. pylori.*

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

Amaç: Son yıllarda H. pylorinin klaritromisine karşı direncinin arttığına dair çok sayıda çalışma bildirilmektedir. Bu çalışmada H.pylori eradikasyonunda en çok kullanılan ilk basamak eradikasyon şemasının güncel başarısının iki farklı proton pompa inhibitörü; pantoprazol ve lansoprazol kullanılarak araştırılması amaçlandı. ***Yöntem:*** *H. pylori pozitif fonksiyonel dispepsisi olan 90 hasta çok merkezli bir çalışmada pantoprazol 2x40mg veya lansoprazol 2x30mg ile birlikte amoksisilin 2xl000mg ve klaritromisin 2x500mg 14 gün süreyle alacak şekilde 2 ayrı gruba randomize edildi. H. pylori histoloji ve hızlı üreaz testi ile belirlendi. Eradikasyon tedavisinden 6 hafta sonra kontrol endokopi yapılarak H. pylori araştırıldı.* ***Bulgular:*** *Yetmişdokuz hasta protokolü tamamladı. Per protokol analizinde pantoprazol, amoksisilin, klaritromisin grubunda %70 (28/40), lansoprazol, amoksisilin, klaritromisin grubunda %69.2 (27/39) eradikasyon saptandı. Tedavi hedeflenen gruptaki eradikasyon oranları pantoprazol, amoksisilin, klaritromisin grubunda %62.2, lansoprazol, amoksisilin, klaritromisin grubunda %60 olarak belirlendi. İki grup arasında eradikasyon oranları açısından fark saptanmadı (p>0.05) Sonuç: H. pylori için halen en popüler olan ve PPI, klaritromisin, amoksisilinden oluşan ilk basamak eradikasyon rejimi bu çalışmada orta derecede bir başarı sağlamıştır. H. pylori eradikasyonunda alternatif tedavilere ihtiyaç vardır. Proton pompa inhibitor seçimi eradikasyonun başarısını etkilememektedir.*

Anahtar kelimeler: *Helicobacter pylori,* eradikasyon, klaritromisin, pantoprazol, lansoprazol

INTRODUCTION

Proton pump inhibitor (PPI)-based triple therapies for 7-14 days were recommended as a first-line treatment option by the European *Helicobacter Pylori* Study Group 1. Amoxicillin and clarithromycin are the most frequently used antibiotics in these protocols. However, these protocols do not always succeed, primarily because of antimicrobial resistance (2-4). Recently, it has been well demonstrated in a number of studies both from Turkey and throughout the world that primary and

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secondary *Helicobacter pylori (H. pylori)* resistance to clarithromycin has increased markedly in the last 10 years (5-8). In addition, regional differences in antibiotic resistance may also change the success rate of these treatments.

The bulk of data with regard to the efficacy of PPI-based *H. pylori* eradication regimens have been generated with omeprazole- or lansoprazole-containing regimens in our population. Pantoprazole has been launched in recent years, but there have not been sufficient studies undertaken in our country to investigate its efficacy. Although there is increasing evidence that the choice of PPI is not important in *H. pylori* eradication, it would be helpful to demonstrate the efficacy of pantoprazole in some regional studies. The aims of the present study were: (i) to assess the current success rate of PPI-based triple regimens including amoxicillin and clarithromycin, and (ii) to compare the efficacy of pantoprazole with lansoprazole in *H. pylori* eradication.

MATERIALS AND METHODS

Patients

Ninety patients with *H. pylori-positive* non-ulcer dyspepsia were enrolled in the study from February 2002 to June 2003. The presence of *H. pylori* was assessed by histological examination and rapid urease test. Patients were eligible for the study if they tested positive for *H. pylori* on both tests. Patients who had taken bismuth salts, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, H_2-receptor blockers, or antimicrobials within the previous four weeks were excluded. Other exclusion criteria were pregnancy, history of penicillin or any other antibiotic allergy and previous gastric surgery. All patients provided written informed consent and the study protocol was approved by the local ethic committees.

Study Design

The study was designed as a single blind, randomized trial involving two centers from Turkey. After the selection procedure, patients were randomly assigned into two study groups using random sampling numbers. The first group of patients (n=45) were given pantoprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg (PAC protocol) twice daily for 14 days, while the second group (n=45) was given lansoprazole 30 mg, amoxicillin 1000 mg and clarithromycin 500 mg (LAC protocol) twice daily for the same duration. Patients were asked to report any side effects during the treatment period. Patient compliance was evaluated at the end of treatment by pill count, and was considered good if more than 80% of the medication had been taken. No PPI or H_2-receptor blockers, only antacids on demand, were permitted prior to follow-up endoscopy, which was performed six weeks after the end of eradication treatment to determine *H. pylori* status. Successful eradication of bacteria was defined as negative histological examination and rapid urease test at the follow-up examination.

Histology

Biopsy specimens (two from the antrum and two from the corpus) were placed into 10% buffered formaldehyde and then embedded into paraffin after tissue processing. Sections were stained by hematoxylin and eosin, and with toluidine for *H. pylori*. An experienced pathologist who was blinded to the clinical information of the patients examined every specimen. The activity of gastritis and density of *H. pylori* colonization were graded according to the Sydney classification on a scale of 0-3: none [0], mild [1], moderate [2], and severe [3] (9),

Statistical Analysis

The demographic and clinical features of the study groups were compared using the Wilcoxon rank sum test. Statistical analyses of the eradication frequency were made by chi-square test with a Yates correction and the Fisher exact test. A p value less than 0.05 was considered statistically significant. All analyses were conducted using a computer based statistics software (SPSS for Windows 8.0, 1997, SPSS Inc. Chicago, USA).

RESULTS

Five patients in the PAC and six patients in the LAC group were dropped from the study because of poor compliance or because they did not return for follow-up endoscopy. No patient discontinued the treatment due to adverse effects. The demographic and clinical characteristics of patients who completed the protocols are shown in (Table 1). The overall eradication rate of *H.pylori* was 69.6% (55 in 79 patients) in the study. The observed eradication rate was very similar in both protocols: 70% in group PAC (28/40) and 69.2% in group LAC (27/39) ($p>0.05$). The eradication rates according to intention to treat (ITT) analysis were 62.2% and 60% in the two groups, respectively ($p>0.05$).

Table 1. Demographic and clinical characteristics of the patients who completed the protocols

Characteristics	Group PAC	Group LAC	P
Number of patients, n	40	39	
Mean age (range), years	45.1 (19-69)	48.3 (28-67)	NS
Male/Female	21/19	17/22	NS
Smoking (>5 cigarettes/day)	14	11	NS
Alcohol use (>1 day/week)	3	5	NS
Antacids	16	11	NS

NS: Non significant, PAC: Pantoprazole-amoxicillin-clarithromycin, LAC: Lansoprazole-amoxicillin-clarithromycin

The grade of *H. pylori* density in eradicated and non-eradicated groups before and after treatment as well as in the PAC and LAC groups are shown in (Table 2). The *H. pylori* density had decreased to grade 0 in all eradicated patients. The median score of *H. pylori* density had decreased from 2 to 1 in non-eradicated patients (n=24). At baseline, the score of gastritis was markedly reduced in the *H. pylori* eradicated group compared to the non-eradicated group ($p<0.05$). There was no difference in the reduction rate of the gastritis score when the LAC and PAC groups were compared ($p>0.05$).

The demographic and clinical features of patients were analyzed to determine the influence of each factor on the outcome of the treatment (Table 3). However, no significant role of these factors could be detected on the eradication rate of *H. pylori.*

Table 2. The distribution of patients by grade of *H. pylori* density before and after tretament in eradicated/non-eradicated groups and in PAC/LAC groups

Groups	Number(i)	Grades (n)			
		0	1	2	3
Eradicated (BT)	55		32	17	6
Eradicated (AT)	55	55	-	-	-
Non-eradicated (BT)	24	-	11	9	4
Non-eradicated (AT)	24	-	15	8	1
PAC group (AT)	40	28	8	3	1
LAC group (AT)	39	27	7	5	0

BT: Before treatment, AT: After treatment

All drugs were usually well tolerated, but 17 patients (21.5%) complained of side effects such as nausea (n: 7), metallic taste (n: 5) and diarrhea (n: 5). No significant difference was observed in the incidence of side effects between groups, and all side effects resolved completely within four days of the end of treatment.

DISCUSSION

The generally accepted minimum eradication rate of treatment regimens to be used for *H. pylori* eradication is 80%. It is also known that the success of these therapies decreases in clinical practice compared to clinical trials (10). The *H. pylori* eradication rates achieved in these two groups were not satisfactory, and can be defined as a moderate success. They were especially lower than those of many European studies, which have reported 85 to 95% eradication rates with the same drugs (11). The recommended duration of treatment with a PPI-based triple regimen is between 7 to 10 days. There is some evidence supporting the superiority of longer treatment in the eradication rate of *H. pylori* (12). In this study, however, an unsatisfactory eradication rate was achieved in spite of a 14-day treatment protocol and good compliance.

There has been a marked decrease in the eradication rate of *H. pylori* with a PPI-based clarithromycin plus amoxicillin regimen in our population from 1996 to 2003 (13). Based on information gained from National Gastroenterology Congresses of Turkey, where most of the national studies

Table 3. The effect of demographic and clinical characteristics of the patients on the eradication rate

Factor	n	Eradication		OR	95% CI	P
		n	(%)			
Age				1.39	0.48-4.06	0.67
<45	44	32	(72.7)			
>45	35	23	(65.7)			
Gender				1.14	0.39-3.32	0.98
Male	38	27	(71.0)			
Female	41	28	(68.2)			
Cigarette						
Smoking	25	14	(56.0)	0.4	0.13-1.24	0.12
Non-smoking	54	41	(75.9)			
Alcohol				0.39	0.07-2.11	0.23
User	8	4	(50.0)			
No alcohol	71	51	(71.8)			
Gastritis						
Grade 1-2	47	35	(74.4)	1.75	0.6-5.17	0.37
Grade 3	32	20	(62.5)			

are presented, the median eradication rate in 1996 was 88% in nine studies including a PPI, clarithromycin and amoxicillin regimen with standard doses and duration, whereas this decreased to a median rate of 68% in nine similar studies including the same drugs in 2003. We have also observed an important decrease in the eradication success of this protocol when compared to some previous studies of our researchers. In 1996, an 88% eradication rate was reached with a seven-day, standard-dose omeprazole, clarithromycin and amoxicillin combination, whereas the same protocol achieved a 69.4% eradication rate in 1999 (14, 15). In the current study, we used the same antibiotics with other PPIs for 14 days instead of seven days, but nevertheless could only achieve the same rate as in our study in 1999. In a current multicenter study of Turkey, in which five centers participated from different regions, a PAC protocol for seven days achieved a 68% eradication rate (16). It is evident from all these data that there has been a significant decrease in the success rate of PPI, clarithromycin and amoxicillin combination for *H. pylori* eradication in our population. Thus, the current success of this protocol should be accepted as unsatisfactory in our community.

High eradication rates, however, continue to be reported in many studies from different countries with a PPI, amoxicillin and clarithromycin protocol (11). Nevertheless, a constant decrease in the eradication success of this combination is also a reality in many geographical regions of the world (17-23). Table 4 summarizes some of the current studies from different countries in which lower eradication rates were achieved with this protocol, similar to our findings.

Antibiotic resistance of *H. pylori* is the most common reason for eradication failure in most of the reports. However, amoxicillin resistance is still absent or very low for *H. pylori* (24). Therefore, it seems the main reason for the low eradication rates with a PPI, amoxicillin and clarithromycin protocol in recent years is related to clarithromycin resistance. In the last 10 years, clarithromycin has been, no doubt, the most widely used antibiotic for *H. pylori* eradication both in our country and throughout the world. It has been used not only for *H. pylori* eradication, but also in a lot of bacterial diseases such as respiratory tract infections. Previous use of clarithromycin is clearly associated with *H. pylori* resistance to this antibiotic (2). A well-designed Japanese study has shown that the proportion of clarithromycin resistance significantly increased in relation to the annual consumption of this drug (25). Many reports in different countries have shown a gradual increase in both primary and secondary resistance of *H. pylori* against clarithromycin (5, 6, 24-27). Although higher rates of eradication continue to be reported, the overall current primary resistance rate to clarithromycin is nearly 10% in Western countries (28). However, there has recently been a more significant increase in the secondary resistance to clarithromycin. Toracchio et al. reported a 23.4% primary and 82.3% secondary clarithromycin resistance from central Italy in a recent report (29). Resistance to clarithromycin was significantly higher in strains isolated from patients from southern European countries than from central and northern Europe in a multicenter study including 22 European centers (28). Some recent studies have shown that the sensitivity of *H. pylori* to clarithromycin also decreased significantly compared to previous years in our population (8, 30-33). The eradication rate of clarithromycin sensitive/resistant strains was 89%/40% in a current European study (34). Differences in the eradication success of clarithromycin sensitive and resistant strains of *H. pylori* in PPI-based protocols have also been reported from different populations (35-37). The prevalence of *H. pylori* resistant strains to clarithromycin varies geographically, and this has been the main cause of the different eradication rates reported in the various studies. The major drawback of our study was being unable to investigate the clarithromycin resistance in *H. pylori*. However, there are enough data showing high primary and secondary clarithromycin resistance from different centers in our population (8, 30-33).

Poor drug compliance, gender, age, smoking, bacterial load and genetic polymorphism for cytochrome P450 are among the suggested predictors of fa-

Table 4. *H. pylori* eradication rates of some current studies using standard doses of PPI plus amoxicillin 1 g and clarithromycin 500 mg twice daily

References	Country	Duration (day)	Rate (%)
Bochenek et al. (17), 2003	USA	7	72
Neri et al. (18), 2003	Italy	7	60
Boixeda et al. (19), 2003	Spain	7	73
Malekzadeh et al. (20), 2003	Iran	7	35.5
Palmas et al. (21), 2002	Italy	7/14	68/72
Tankovic et al. (22), 2001	France	7	67
Perri et al. (23), 2001	Italy	7	67

ilure of *H. pylori* eradication with standard therapy (23, 38). The patients' suspected lack of compliance was not included in this study, and those patients with poor compliance were removed from the study. The eradication rate was not significantly different between smoking/non-smoking, male/female and young/older patients. Thus, we could detect no factor to explain the moderate eradication success from the demographic and clinical data of the patients. CYP2C19 genotyping could not be investigated in this study. However, pantoprazole, which has a lower induction potential on CYP, was used, and no difference in the eradication rate compared to that with lansoprazole was detected. Furthermore, current data in the literature has mostly rejected the influence of CYP2C19 genotyping on the eradication outcome (36, 39).

The choice of PPI in *H. pylori* eradication protocols when used in two doses and with the same antibiotics would seem to not be important in the success of the eradication and tolerability of the treatment (11, 40). In this study, as in many previous ones, we detected no difference between pantoprazole and lansoprazole including study arms. Thus, the preference for PPI in the eradication regimens should depend on availability, possible drug interactions and cost of the drug, rather than on proven superiority of a particular compound.

In conclusion, the success of the first-line and most popular PPI-based clarithromycin and amoxicillin eradication regimen is tending to decrease, probably due to rising antibiotic resistance. Patients in whom the eradication of *H. pylori* is essential, such as in those with peptic ulcer, should be evaluated for a second-line therapy not containing clarithromycin, in the case the first-line treatment failed. Furthermore, development of new protocols which do not include clarithromycin are needed as a first-line therapy for *H. pylori* eradication. Pantoprazole is as effective as lansoprazole in *H. pylori* eradication. Thus, the choice of PPI is not important in the PPI-based triple protocols.

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