Modified sequential Helicobacter Pylori eradication therapy using high dose omeprazole and amoxicillin in the initial phase in the extensive metaboliser turkish patients for CYP2C19 polymorphism is ineffective

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Abstract

Aim : **To investigate whether the sequential therapy composed of high dose omeprazole and high dose amoxicillin in the first step was effective in eradication of H. pylori and whether there was a relation between effectiveness of the therapy and CYP2C19 gene polymorphism.**

Method : **134 dyspeptic patients with H. pylori were administered a modified sequential therapy composed of omeprazole 40 mg t.i.d. and amoxicillin 1000 mg t.i.d. for the first five days followed by omeprazole 20 mg b.d., metronidazole 500 mg t.i.d. and tetracycline 500 mg t.i.d. for the next five days. CYP2C19 genotype status was determined in patients. Hp eradication status was investigated by C^{14} UNT four weeks after treatment.**

Results : **The eradication rates were 64,9% in ITT and 74,3% in PP analysis. In subgroup analyses, eradication rates were 73,8% and 60,8% (p : 0,145) in ITT for peptic ulcer and non-ulcer dyspepsia patients respectively and 86,1% and 69,1% (p : 0,052) in PP analysis for peptic ulcer and non-ulcer dyspepsia patients respectively. The difference was not significant. As for the CYP2C19 gene status, 81,5% of the patients had HoEM and 17,3% of the patients had HeEM, and eradication rates were 72% and 75% in ITT analysis for HoEM and HeEM respectively (p : 0.803) and 73.9% and 85.7% in PP analysis for HoEM and HeEM respectively (p : 0.347). There was not a significant difference in H. pylori eradication rates between the two groups.**

Conclusion : **This modified high-dose sequential therapy was ineffective in a Turkish sample, nearly all of whom had EM in terms of CYP2C19 gene status.** (Acta gastroenterol. belg., **2014**, 77, **3-7**).

Key words : Helicobacter pylori, sequential therapy, dual therapy, German treatment, CYP2C19.

Introduction

Helicobacter pylori (*H. pylori*) infection can be considered an important health problem in Turkey due to its high frequency in the Turkish population. The estimated prevalence of *H. pylori* infection is approximately 81% in our country (1-3). Maastrich-4 Consensus guidelines recommend triple therapy initially (4). Quadruple therapy is recommended for treatment failures or when the prevalence of antibiotic-resistant *H. pylori* is known to be high in a population. Indeed, eradication rates for these schemes have been 45%-60% (5-8).

Recent studies have suggested that sequential (two-step) quadruple therapy in which amoxicillin and a PPI are given for 5 days followed by a PPI plus clarithromycin and tinidazole appeared excellent in terms of cure rates (e.g. 90% or greater) (9-13). Therefore, we attempted to implement a new treatment scheme consisting of sequential administration of pantoprazole 40 mg bid plus amoxicillin 1 gr bid for 7 days followed by pantoprazole 40 mg bid plus metronidazole 500 mg t.i.d., and tetracycline 500 mg t.i.d. for 7 days (14). The result of this therapy for the first-line treatment of *H. pylori* was disappointing. Meanwhile, Graham published a pilot study that investigated a new sequential therapy consisting of a high-dose amoxicillin (e.g. 1 g three times daily) and a high-dose esomeprazole (40 mg three times daily) for 5 days followed by gatifloxacin 400 mg once daily for seven additional days (three drugs for the final 7 days). It helped to eradicate the disease successfully (15). A high dose of PPI and amoxicillin was used as initial therapy based on a study from Germany showing that a high-dose PPI and high-dose amoxicillin produced high rates of success (16,17).

Host background in the genotypes of S-mephenytoin 4'-hydroxylase (CYP2C19) may predict the outcome of PPI-based therapy (18,19). Currently available PPIs are mostly metabolized by CYP2C19 of the p450 enzyme system in the liver, and hence a more rapid PPI clearance in the extensive metabolizer (EM) is presumed to have a poorer *H. pylori* eradication outcome than the poor metabolizer (PM) (20-22).

Therefore, we decided to use a high-dose PPI and high-dose amoxicillin in the first step of the sequential therapy. Based on the results of a study from Germany, we used omeprazole as a PPI. Our primary aim was to test whether an increased dosage of omeprazole and amoxicillin in the initial phase of sequential therapy can have an improved *H. pylori* eradication rate, and our secondary aim was to evaluate the effectiveness of therapy in relation to CYP2C19 genotype polymorphism.

Methods

This was a prospective, open-label, single-centre study of the treatment of patients with *H. pylori* infection referred to our department. The patients who suffered

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from a serious illness, those who underwent gastric surgery before, diabetics, those who received antibiotics, bismuth or PPI for the past two months and those who were given treatment for eradication of *H. pylori* before were not included in the study. History was taken from all patients. They were also subjected to physical examination and routine laboratory investigations. The study was approved by the Ethics Committee of Mersin University. All patients signed an informed consent prior to therapy.

Endoscopy, Histology and Diagnosis of H. pylori *Infection*

During endoscopy, two biopsies were obtained for histological evaluation (one from the antrum and one from the corpus). Results of histopathological examinations were evaluated according to the Sydney classification. An antrum biopsy was obtained for the rapid urease test which was a non-commercial test prepared in our microbiology department. ^{14}C-urea breath test (UBT) was performed. The patients were regarded as infected when all tests were positive.

Treatment

All patients received omeprazole 40 mg t.i.d. and amoxicillin 1000 mg t.i.d. for 5 days, and omeprazole 20 mg b.d., metronidazole 500 mg t.i.d. and tetracycline 500 mg t.i.d. for the following 5 days. Four weeks after the completion of the therapy, eradication was confirmed by ^{14}C-UBT.

Compliance was considered good when the patients took more than 95% of the prescribed drugs appropriately and on time. Side effects in this study were evaluated using a questionnaire and by patient interview after the completion of antimicrobial therapy (23).

Testing for CYP2C19 Genotype Polymorphisms

CYP2C19 Genotype analysis was performed described by Ghodke *et al*. (24).

Statistical Analyses

The success rate was considered as the percentage of patients whose *H. pylori* infection was cured. Analyses of the data obtained were performed on an intention to-treat (ITT) and a per-protocol (PP) basis. All patients were included in the ITT analysis. Those patients who were lost to follow-up, violated the protocol or were poorly compliant due to side effects were considered drop-outs and excluded from the PP analysis.

Student's t-test was used for the parametric comparison between the groups. Chi-square test was used for non-parametric comparisons. The relative risk with a 95% confidence interval was used to analyze whether there was a difference in eradication rates by ITT and PP analyses between the groups. All the statistical tests were two-sided. $P < 0.05$ was considered significant.

Table 1. — **Demographic and clinical characteristics and genotype of CYP2C19 of the study patients**

	Total patients (n: 134)
Mean age (years)	46,4 ± 15,8
Male/Female ratio	36/98
Endoscopic findings	
Gastric ulcer	14
Duodenal ulcer	28
Antral gastritis	53
Pangastritis	15
Atrophic gastritis	19
Erosive gastritis	2
Alkaline reflux gastritis	1
Gastric polyp	1
Compliance *	
Good	117
Poor	6
CYP2C19 genotypes**	
HoEM	75
HeEM	16
PM	1

*Eleven patients who lost to follow up were excluded from the analysis.

**Some proportion of the patients declined to give blood for genotyping. The results were based on the data about the patients who accepted to give blood for the tests.

Results

A total of 134 patients were included in the study. Table 1 presents age, gender, endoscopic findings, drug compliance and results of CYP2C19 genotyping. The results were based on the data about the patients who accepted to give blood for the tests. 92 patients (69%) accepted genotype analysis. Out of all these patients, 98.9% (91/92) had genotypes of CYP2C19 as EM and 81.5% of them had homozygous extensive metabolizer (HoEM). Only one patient had PM. In this series, the study group achieved a > 90% rate of well-to-full compliance. Only 6 patients had poor drug compliance. Two patients took all their drugs in the first step, but one of them did not take his drugs regularly and two of them discontinued treatment due to side-effects (one had nausea and abdominal pain and the other had sleepiness).

Causes of exclusion from per-protocol analysis and adverse events of therapy

All 134 patients were enrolled for ITT analysis to determine the eradication rate of the therapy. Apart from the above-mentioned 6 patients with poor drug compliance, 11 patients did not return for the follow-up. Excluding these 17 patients, 117 patients were enrolled for PP analysis. Table 2 shows adverse effects and the total number of adverse events during the *H. pylori* eradication period. As mentioned above, only two patients discontinued treatment due to side-effects.

Table 2. — **Side effects of the therapy**

	Total events (%)
Nausea	10 (15,8)
Vomiting	2 (3,1)
Constipation	3 (4,7)
Diarrhoea	4 (6,3)
Metallic taste	4 (6,3)
Bitterness of mouth	4 (6,3)
Headache	9 (14,2)
Abdominal pain	7 (11,1)
Lack of appetite	8 (12,6)
Distension	6 (9,5)
Drowsiness	1 (1,5)
Weakness	2 (3,1)
Dizziness	2 (3,1)
Dry mouth	1 (1,5)
Total events	63

*Eleven patients who lost to follow up were excluded from the analysis.

Eradication results of high-dose sequential therapy for H. pylori *infection*

H. pylori eradication rate was 64,9% in ITT, and 74,3% in PP analysis. As shown in Table 3, there were no differences in the *H. pylori* eradication rates between patients with HoEM and HeEM genotypes of CYP2C19 in the study group. There was only one patient with PM in the study group and the disease was eradicated in this patient. Since he was the only patient with PM, he was not included into the analysis. Subgroup analyses showed eradication rates of 73.8% and 60.8% in peptic ulcer (PU) and non-ulcer dyspepsia (NUD) groups (p : 0,145) in ITT analysis respectively. However, in the PP analysis, the eradication rates were 86.1% and 69.1% in peptic ulcer (PU) and non-ulcer dyspepsia (NUD) groups (p : 0.052) respectively. The *H. pylori* eradication rate, related to CYP2C19 genotype polymorphism between the PU group and the NUD group, was not statistically significant [ITT analysis : 83% vs. 67%, (p : 0.134) for HoEM, 100% vs. 69% (p : 0.267) for HeEM ; PP analysis : 83% vs. 69% (p : 0.202) for HoEM, 100% vs. 81% (p : 0.425) for HeEM in PU and NUD groups respectively].

Discussion

Common causes of failure of *H. pylori* eradication therapy are antimicrobial resistance, drug compliance and increased bacterial loads (25,26). A large bacterial load in infected stomachs results in the inoculum effect (27). Even though development of spontaneous resistance may be low, a large number of organisms present (e.g. > 10^9) make it likely that a small population of resistant organisms may be present at any time (27,28). Theoretically, sequential therapy can prevent or reduce the development of the disease as it can reduce the chance of outgrowth of an existing population of resistant organisms. After suppression of the bulk of the bacterial load, the small remaining population of *H. pylori* can theoretically be eliminated following the addition of the remaining antibiotic(s). Amoxicillin is a reasonable choice as it is an effective antibiotic against *H. pylori* and resistance is rare even after treatment failure. An antisecretory drug is also required for amoxicillin to be effective in the stomach.

This study yielded two results. First, although we increased dosages of PPI and the antibiotic we used in the initial phase of the sequential therapy through which we obtained very low eradication rates before, unfortunately we could not achieve acceptable eradication rates. Although PPIs used in our previous and present studies were different, there were many studies showing that similar doses of different PPIs yielded similar eradication rates (29,30). In fact, we found in another study performed in the same study area as the present study that several standard triple therapy regimes consisting of omeprazole, lansoprazole and pantoprazole had similar eradication rates (5). Therefore, we preferred omeprazole since it was used in the original German study and since it was the most inexpensive PPI.

The second result of this study was that as shown in Table 1, the CYP2C19 genotype was EM in almost all the patients and that most of them had HoEM. As shown in Table 1, EM, especially HoEM, was the dominant genotype, which is consistent with the results of a large scale study on healthy individuals we performed. In fact, there was only on patient with PM of CYP2C19 in the present study. The rates of CYP2C19 gene polymorphism in the study area were as follows : 72,1% of the people had HoEM, 20,7% HeEM and 3,6% PM (3,6% unidentified) (31). Substantial ethnic differences have been reported in the incidence of the EM or PM genotype of CYP2C19. The frequency of PM genotype is much lower (3% to 5%) in white U.S. or European populations as in Turkey than in Asian persons (18% to 23%) (32,33).

PPIs, such as omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole are mainly metabolized

Table 3. — **Impact of CYP2C19 genotypes on H. Pylori eradication rates**

Genotype eradication rate	HoEM	HeEM	PM	P values
Intention-to-treat	54/75 (72%)	12/16 (75%)	1/1 (100%)	0.803
Per-protocol	54/73 (73,9%)	12/14 (85,7%)	1/1 (100%)	0.347

*: P values belong to the evaluation of HoEM and HeEM groups.

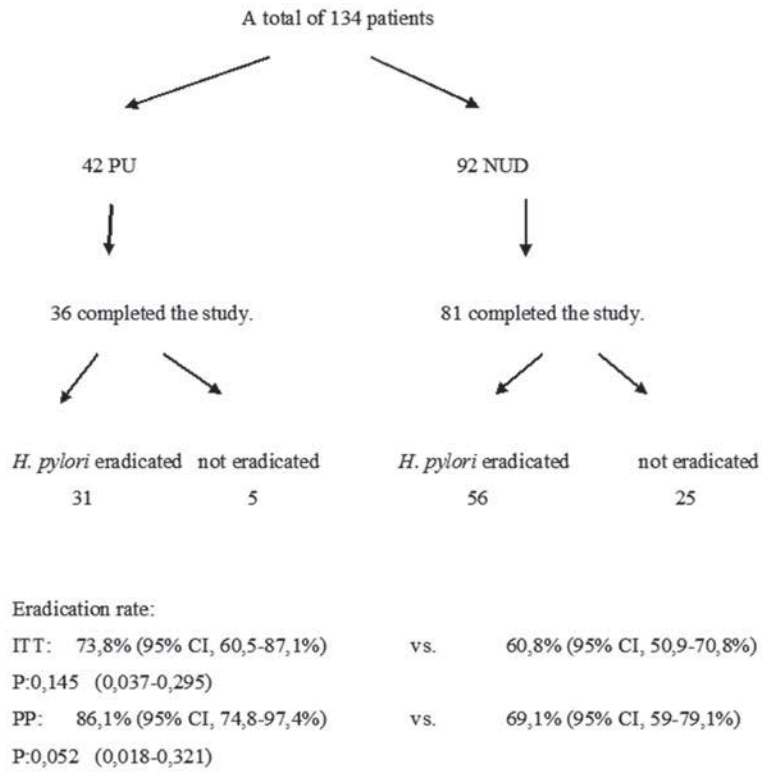

Fig. 1. — Flowchart showing the number of patients enrolled in the study and the subsequent analyses made to investigate eradication of *H. Pylori*.

by CYP2C19 in the liver. There are genetically determined differences in the activity of this enzyme. The genotypes of CYP2C19 are classified into three groups : rapid extensive metabolizer, intermediate metabolizer, and poor metabolizer, corresponding to HoEM, HeEM and PM repectively (34,35). The pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status. Plasma PPI levels and intragastric pH during PPI treatment in the HoEM are lowest, those in the HeEM group come next, and those in the PM group are the highest of the three groups. These CYP2C19 genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs influence cure rates for the gastro-esophageal reflux disease and *H. pylori* infection by PPI-based therapies. For a better PPI-based treatment, doses and dosing schemes of PPIs should be optimized based on CYP2C19 genotype status (36). A more frequent daily dosing of a PPI can achieve a sufficient acid suppression in the HoEM genotype group as noted above (37,38). The low eradication rate in the present study can be explained by the fact that almost all the patients had EM.

The eradication rates for *H. pylori* by dual omeprazole and amoxicillin therapy are around 30% in HoEM, 60% in HeEM, and 100% in PM groups (39). However, Bayerdorffer and associates reported that dual therapy with high dosages of omeprazole (40 mg three times daily) and amoxicillin (750 mg three times daily) could achieve a cure rate of 91% in white persons, even though most of the patients probably had EM genotypes (16). A dose of at least 120 mg of omeprazole in dual therapy may therefore be required to achieve a sufficiently high cure rate of *H. pylori* infection in persons with EM genotypes. However, we failed to obtain sufficient eradication rates although we employed increased doses of both PPI and amoxicillin.

The results of this study do not allow us to comment about the effects of our sequential therapy on PM genotypes since only one patient in the present series had PM genotype.

As shown in Table 2, side effects were usually self-limited. There was a minor influence on the dropout rate or even the rate of complete compliance to the therapy. Only two patients stopped receiving therapy due to its side-effects. These findings confirm that the use of high-dose sequential therapy could be well tolerated with a good compliance.

One limitation of the present study was that we did not perform culture for *H. pylori* and tests for resistance to antibiotics. However, it has been agreed that there is little or no resistance to amoxicillin and tetracycline, though whether resistance to these antibiotics might have played a role in low eradication rates is not clear.

In conclusion, this modified sequential therapy with high-dose omeprazole and high-dose amoxicillin in the initial phase of the treatment schema was not sufficiently successful in eradication of *H. pylori* in a Turkish population most of whom had CYP2C19 EM genotype.

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