Correlation of CYP2C19 Genetic Polymorphisms With *Helicobacter pylori* Eradication in Patients With Cirrhosis and Peptic Ulcer

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Background: To investigate whether or not *CYP2C19* genotype status is associated with cure rate for *Helicobacter pylori* infection in patients with cirrhosis and peptic ulcer, achieved with 2 weeks of triple therapy with rabeprazole, amoxicillin and clarithromycin.

Methods: We prospectively studied 95 consecutive patients with cirrhosis and *H. pylori*-infected active peptic ulcers. *H. pylori* infection was confirmed if any 2 of the following were positive: *H. pylori* DNA, histology, and rapid urease test. Patients were assigned to an open-label 2-week course of oral amoxicillin 1,000 mg b.i.d., rabeprazole 20 mg b.i.d. and clarithromycin 500 mg b.i.d. Subsequently, all patients received oral rabeprazole 20 mg once daily until week 8. Three months and 1 year after therapy, all patients with cirrhosis were followed up endoscopically for peptic ulcer, rapid urease test, and ^{13}C-urea breath test. The *CYP2C19* genotype status for 2 mutations associated with the extensive metabolizer phenotype was determined by polymerase chain reaction and restriction fragment length polymorphism analysis.

Results: Cure rates for *H. pylori* infection were 80.9% (95% CI, 22.8–88.6%), 89.8% (95% CI, 50.8–90.2%), and 100% (95% CI, 62.8–100%) in the rapid-, intermediate-, and poor-metabolizer groups, respectively. Healing rates for duodenal and gastric ulcer in the 3 groups were roughly parallel with cure rates for *H. pylori* infection.

Conclusion: The results of the genotyping test for *CYP2C19* seem to predict cure of *H. pylori* infection and peptic ulcer in patients with cirrhosis who receive triple therapy with rabeprazole, amoxicillin, and clarithromycin. [*J Chin Med Assoc* 2010;73(4):188–193]

Key Words: cirrhosis, CYP2C19, *Helicobacter pylori* eradication, peptic ulcer

Introduction

The disease phenotypes of *Helicobacter pylori* infection include gastritis (80–85%), peptic ulcer (10–15%), gastric adenocarcinoma (1–2%), and gastric mucosa-associated lymphoid tissue lymphoma (<0.01%). Currently, eradication of *H. pylori* can decrease the recurrence of peptic ulcer and gastric mucosa-associated lymphoid tissue lymphoma, potentially prevent the development of gastric cancer, and be beneficial in a certain number of cases of functional dyspepsia.[1] The variable clinical outcomes of *H. pylori* infection are attributed to the variation in extent and severity of gastric inflammation, with resultant differences in gastric acid secretion.[2,3] A complex interaction of host and microbes that leads to chronological changes in pattern of gastritis and gastric acid secretion is the gateway to understanding the pathogenesis of *H. pylori*-related gastroduodenal disorders. Age at infection, environmental cofactors (e.g. nutrition), host genetic status, and microbial virulence are factors that influence the above interaction.[4,5]

To date, the real role of chronic *H. pylori* infection in patients with cirrhosis and upper gastrointestinal

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bleeding is still uncertain. However, a high prevalence of *H. pylori* in patients with liver cirrhosis has been found.[6–10] Eradication of *H. pylori* is very efficacious in the treatment of various upper gastrointestinal diseases.[11] Current strategies for the cure of *H. pylori* infection include triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin or metronidazole,[12] but the development of resistance of *H. pylori* to the latter 2 drugs has been reported.[13] Therefore, an understanding of the determinants of the success or failure of attempts to cure *H. pylori* infection with triple therapy is clinically important.

Hepatic drug oxidation is a major source of interindividual variations in pharmacokinetics and therapeutic response. The discovery of polymorphic oxidative metabolism of S-mephenytoin 4′-hydroxylation via *CYP2C19* has opened up a new discipline in the study of drug metabolism.[14,15] Proton pump inhibitors such as omeprazole and rabeprazole are widely used as acid-inhibitory agents for the treatment of acid-related diseases (e.g. peptic ulcer, and gastroesophageal reflux disease).[16] Moreover, a *CYP2C19* genotype-dependent difference in rabeprazole pharmacodynamics has been demonstrated.[17] On the basis of this assumption, we prospectively studied whether or not differences in *CYP2C19* genotype status would affect cure rates for *H. pylori* infection and peptic ulcer in patients with cirrhosis who received triple therapy with rabeprazole, amoxicillin and clarithromycin.

Methods

Adult patients diagnosed with cirrhosis between January 2002 and December 2006 were evaluated. Inclusion criteria were: (1) no known previous bleeding from the upper gastrointestinal tract; (2) cirrhosis with no other disease (e.g. cancer) that reduced life expectancy; and (3) cirrhosis with no known antibiotic resistance, especially to clarithromycin, or very poor compliance. Ten patients with bleeding diathesis, chronic obstructive lung disease, heart disease or renal disease were excluded from the study.

Functional hepatic reserve was classified according to the Pugh-modified Child's classification. The patients in Child–Pugh class A were defined as having compensated cirrhosis; the patients in Child–Pugh classes B and C were defined as having decompensated disease. The study sample consisted of 95 patients with cirrhosis and gastric ulcer ($n=48$) or duodenal ulcer ($n=47$). Seventy-one patients were male, and 24 were female, with a mean age (± standard deviation) of 46.5 ± 6.0 years. All were positive for *H. pylori* on rapid urease testing. For the treatment of *H. pylori*-infected active peptic ulcers, all patients were assigned to an open-label 2-week course of oral amoxicillin 1,000 mg twice daily (b.i.d.), clarithromycin 500 mg b.i.d., and rabeprazole 20 mg b.i.d.

Patient adherence to therapy and occurrence of side effects were assessed by interviews. Gastroduodenoscopy and determination of *H. pylori* infection were done before and 3 months after treatment. Endoscopists were blinded to patient treatment status and genotypes. Written informed consent was obtained from each patient before the study began, and our protocol was approved by the hospital's Human Institutional Review Board. During gastroduodenoscopy, we performed routine inspection of the upper gastrointestinal tract, and biopsy specimens were taken from the antrum for rapid urease testing.[18] All patients also underwent ^{13}C-urea breath testing. Failure to cure *H. pylori* infection was defined as a positive result on any of these tests.

Genotyping procedures that identified wild-type (wt) *CYP2C19* gene and the 2 mutated alleles, *CYP2C19*m1 in exon 5 and *CYP2C19*m2 in exon 4, were performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis, as described by de Morais and colleagues,[19,20] with minor modifications as described by Kubota and coworkers.[21] Extracted genomic DNA was dissolved in distilled water (DNA solution). Genotyping procedures for identifying the wt *CYP2C19* gene and the 2 mutated alleles, *CYP2C19*m1 and *CYP2C19*m2, were carried out by PCR-restriction fragment length polymorphism analysis with allele-specific primers. Genomic DNA (200 ng) was amplified in 1 × PCR buffer [67 mM Tris-HCl, pH 8.8, 17 mM $(NH_4)_2SO_4$, 10 mM β-mercaptoethanol, 7 μM EDTA, 0.2 mg/mL bovine serum albumin] that contained 50 μM dATP, dCTP, dGTP and dTTP, 0.25 μM PCR primers, 2.5 U AmpliTaq DNA polymerase (Perkin Elmer Cetus, Norwalk, CT, USA), and 3.0 mM $MgCl_2$. The forward primer (5′-TATTATTATCTGTTAACTAATATGA-3′) annealed in exon 3, 78 base pairs (bp) upstream from the exon 4/intron 3 junction, and the reverse primer (5′-ACTTCAGGGCTTGGTCAATA-3′) annealed in intron 4, 88 bp downstream from the exon 4/intron 4 junction. Amplification was performed using a Perkin Elmer thermocycler, for 35 cycles of denaturation at 94°C for 1 minute, annealing at 53°C for 30 seconds, and extension at 72°C for 30 seconds. An initial denaturation step at 94°C for 5 minutes and a final extension step at 72°C for 5 minutes were also performed. For sequencing, the PCR product was purified using Microcon and Amicon (Millipore Corp.,

Billerica, MA, USA) columns, and an aliquot was used in the cycle sequencing reaction that used fluorescence-tagged dye terminators (PRISM; Applied Biosystems Inc., Foster City, CA, USA), the same forward primer used in the PCR, and an automated sequencer (Applied Biosystems Inc.).

For detection of *CYP2C19*m1 in exon 5 and *CYP2C19*m2 in exon 4, genomic DNA (200 ng) was amplified in PCR buffer (50 μL) that contained 10 mmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, 0.01% gelatin dNTP mix (dATP, dCTP, dGPT and dTTP; 200 μmol/L final concentration; Takara Shuzo Co. Ltd., Shiga, Japan), 0.2 μmol/L PCR primers, 1.25 U AmpliTaq DNA polymerase (Hoffmann-La Roche Ltd., Basel, Switzerland), and 1.5 mmol/L $MgCl_2$. Amplification was carried out with an automatic thermal cycler (DNA Thermal Cycler PJ 2000; Perkin Elmer) for 40 cycles of denaturation at 94°C for 1 minute, annealing at 57°C for 1 minute, and extension at 72°C for 2 minutes. An initial denaturation step at 94°C for 5 minutes and a final extension step at 72°C for 5 minutes were also performed. Restriction enzyme cleavage was conducted at 37°C for 1 hour after the addition of 25 U *Msp*I for *CYP2C19*m1 and 25 U *Bam*HI for *CYP2C19*m2. The digested PCR products were analyzed on 3% agarose gels and stained with ethidium bromide.

Numerical data are given as the mean ± standard deviation. Statistical differences in mean age, body weight, ratio of gastric to duodenal ulcers, and cure rates for *H. pylori* infection among the genotype groups were determined by using one-way analysis of variance and Fisher's exact test. A p value of < 0.05 was considered statistically significant.

Results

All patients completed the study according to the protocol. Their clinical characteristics are presented in Table 1. Adherence to the prescribed medication regimen was 100% in 42 patients, about 90% in 38 patients, and about 75% in 15 patients. *H. pylori* was eradicated in 100%, 86% and 80% of patients whose adherence was 100%, 90% and 75%, respectively.

Five different combination patterns were noted in the 95 patients. Forty-two were homozygous for the wt alleles (rapid-metabolizer group) in both exon 5 and exon 4 (wt/wt); 20 were heterozygous for the *CYP2C19*m1 mutation without the *CYP2C19*m2

Table 1. Clinical characteristics*

	Group 1 ($n = 42$)	Group 2 ($n = 38$)	Group 3 ($n = 15$)	p
Age (yr)	49.5 ± 5.5	46.8 ± 4.8	48.7 ± 6.3	NS
Sex (M/F)	32/10	29/9	10/5	NS
Etiology				NS
Alcoholism	11 (26)	10 (26)	3 (20)	NS
Viral hepatitis	28 (66)	25 (65)	11 (73)	NS
Others†	3 (7)	3 (8)	1 (6)	NS
Child–Pugh class				NS
A	29 (69)	26 (66)	11 (73)	NS
B	10 (23)	9 (25)	3 (20)	NS
C	3 (7)	3 (8)	1 (6)	NS
Child–Pugh score	8.3 ± 1.6	8.2 ± 1.7	8.1 ± 1.8	NS
Prothrombin time (sec)	20.3 ± 4.5	21.4 ± 4.7	21.2 ± 4.6	NS
Albumin (g/dL)	2.8 ± 0.6	2.9 ± 0.8	2.8 ± 0.7	NS
Bilirubin (mg/dL)	2.7 ± 2.1	2.8 ± 2.2	2.7 ± 2.0	NS
Hemoglobin (g/dL)	8.7 ± 2.7	8.9 ± 2.8	8.8 ± 2.6	NS
Ascites present	6 (14)	5 (13)	2 (13)	NS
Serum alanine transferase (U/L)	105 ± 60	110 ± 58	114 ± 7.2	NS
Follow-up period (mo)‡	35.4 ± 19.6	34.8 ± 18.8	35.2 ± 19.2	NS

**Data are presented as mean ± standard deviation or n or n (%); †includes primary biliary cirrhosis and cryptogenic cirrhosis; ‡only those who were followed for > 30 days are included. NS = not significant.*

mutation (wt/*CYP2C19*m1); 18 were heterozygous for the *CYP2C19*m2 mutation without *CYP2C19*m1 mutation (wt/*CYP2C19*m2); 20 were heterozygous for the *CYP2C19*m1 mutation and the *CYP2C19*m2 mutation (*CYP2C19*m1/*CYP2C19*m2); and 35 were homozygous for the *CYP2C19*m1 mutation without the *CYP2C19*m2 mutation (*CYP2C19*m1/*CYP2C19*m1). All patients were arbitrarily classified into 3 genotype groups: group 1 was the non-mutation group (wt/wt) ($n=42$); group 2 was the 1-mutation group (wt/*CYP2C19*m1 or wt/*CYP2C19*m2) ($n=38$); and group 3 was the 2-mutation group (*CYP2C19*m1/*CYP2C19*m1 or *CYP2C19*m1/*CYP2C19*m2) ($n=15$) (Table 2). The *CYP2C19* phenotypes of groups 1, 2 and 3 corresponded to the rapid-extensive, intermediate-extensive, and poor-metabolizer phenotypes of *CYP2C19*, respectively.

H. pylori infection was cured in 86 of the 95 patients [90.5%; 95% confidence interval (CI), 22.7–87.5%]. The cure rates of *H. pylori* infection for the 3 genotype groups are shown in Table 3. The cure rate was highest in group 3, intermediate in group 2, and lowest in group 1. Ulcer healing was achieved in 40 of the 48 patients with cirrhosis and gastric ulcer, and 41 of the 47 with duodenal ulcer. In patients in whom *H. pylori* infection was cured, all ulcer lesions were healed at follow-up endoscopic examination. Ulcer healing rates for patients with cirrhosis and gastric ulcer in groups 1, 2 and 3 were 80% (95% CI, 38.9–85.6%) (16 of 20 patients), 90% (95% CI, 69.9–99.8%) (18 of 20 patients), and 100% (95% CI, 70.8–100.0%) (all 8 patients), respectively. Ulcer healing rates for patients with cirrhosis and duodenal ulcer were 81.8% (95% CI, 36.8–97.6%) (18 of 22 patients), 88.8% (95% CI, 62.6–98.8%) (16 of 18 patients), and 100% (95% CI, 75.8–100.0%) (all 7 patients), respectively.

Discussion

Hepatic drug oxidation is a major cause of interindividual variations in pharmacokinetics and therapeutic response. The expression of individual P450 proteins in the liver is influenced by a number of factors such as genetic make-up, disease, aging, and environmental factors (smoking, alcohol, nutrition and pollutants). As the metabolism of proton pump inhibitors is mainly catalyzed by *CYP2C19* and *CYP3A4*,[22] genetic polymorphism of *CYP2C19* could be of clinical concern in the treatment of acid-related diseases with proton pump inhibitors.[14]

Oxidation shows considerable interethnic difference; 2–6% of Caucasians and 1% of African–Americans

Table 2. Demographic and clinical characteristics of 95 patients with cirrhosis and peptic ulcer in 3 genotype groups

Variable	Group 1 ($n=42$)	Group 2 ($n=38$)	Group 3 ($n=15$)	*p*
CYP2C19 (status)	wt/wt	wt/m1* or wt/m2†	m1/m2‡ or m1/m1§	
Mean age ± SD (yr)	49.5 ± 5.5	46.8 ± 4.8	48.7 ± 6.3	NS
Mean weight ± SD (kg)	65.7 ± 7.9	63.6 ± 5.9	64.8 ± 8.6	NS
Gastric ulcer/duodenal ulcer (*n*/*n*)	20/22	20/18	8/7	NS

**Heterozygous for CYP2C19m1 without CYP2C19m2; †heterozygous for CYP2C19m2 without CYP2C19m1; ‡heterozygous for CYP2C19m1 and CYP2C19m2; §homozygous for CYP2C19m1 without CYP2C19m2. m1 = CYP2C19 mutation in exon5; m2 = CYP2C19 mutation in exon 4; wt = wild-type; NS = not significant.*

Table 3. Cure rates of *Helicobacter pylori* infection in 3 genotype groups*

Type of ulcer	Cure rate of *H. pylori* infection (95% CI)			*p*
	Group 1 ($n=42$)	Group 2 ($n=38$)	Group 3 ($n=15$)	
	← % (*n*/*n*) →			
Gastric ulcer†	80.0 (16/20)	90.0 (18/20)	100 (8/8)	< 0.05
Duodenal ulcer‡	81.8 (18/22)	88.8 (16/18)	100 (7/7)	< 0.05
Total§	80.9 (34/42)	89.8 (34/38)	100 (15/15)	< 0.001

**Group 1 was the non-mutation group, group 2 was the 1-mutation group, and group 3 was the 2-mutation group; †$p < 0.05$ for group 1 compared with group 2, $p < 0.05$ for group 1 compared with group 3, $p < 0.05$ for group 2 compared with group 3 (Fisher's exact test); ‡$p < 0.05$ for group 1 compared with group 2, $p < 0.05$ for group 1 compared with group 3, $p < 0.05$ for group 2 compared with group 3 (Fisher's exact text); §$p < 0.05$ for group 1 compared with group 2, $p < 0.05$ for group 1 compared with group 3, $p < 0.05$ for group 2 compared with group 3 (Fisher's exact test). CI = confidence interval.*

have been identified as carrying the PM phenotype, whereas its frequency is 19–23% in Japanese, 15% in Chinese and 13% in Koreans.[23] This defect (referred to as *CYP2C19*m1) is common in Asian and Caucasian populations.[21]

Our study shows that rates of cure of *H. pylori* infection in our patients depended on *CYP2C19* genotype patterns. In the poor-metabolizer group (patients with *CYP2C19*m1/*CYP2C19*m1 or *CYP2C19*m1/*CYP2C19*m2), triple therapy with 20 mg rabeprazole, 1,000 mg clarithromycin and 2,000 mg amoxicillin for 2 weeks seemed to be fully effective in curing *H. pylori* infection.

There are several reasons why triple therapy achieves greater success in curing *H. pylori* infection in patients with the poor-metabolizer genotype (group 3) than in those with the extensive-metabolizer genotypes (groups 1 and 2). First, because the metabolic disposition of rabeprazole is genetically determined by *CYP2C19* enzyme activity, the plasma concentration–time curve of rabeprazole (that is, the systemic availability of the drug in the circulation) is markedly increased in persons with the poor-metabolizer phenotype or genotype of *CYP2C19*.[17,22] Consequently, the duration of high intragastric pH levels is longer in patients with the poor-metabolizer genotype than in those with the extensive-metabolizer genotypes. Second, because amoxicillin is unstable and its antibacterial activity is decreased under low pH conditions, increasing the intragastric pH to neutral levels by *H. pylori* infection, and an increased acid-inhibitory effect of rabeprazole, could contribute to the excellent ulcer healing rates seen in patients with the poor-metabolizer genotype of *CYP2C19*, who had either gastric or duodenal ulcer disease. Substantial ethnic differences have been reported in the incidence of the poor-metabolizer genotype, much lower (3–5%) in white American or European populations than in Japanese (18–23%).[24–26] Thus, it seems reasonable that triple therapy with rabeprazole (20–40 mg/day) and amoxicillin (2,000 mg/day) has generally not achieved adequate cure rates for *H. pylori* infection and ulcer disease in these American and European populations.[22] However, some authors have reported that dual therapy with high doses of omeprazole (40 mg 3 times daily) and amoxicillin (750 mg 3 times daily) could achieve a cure rate of 91% in these populations, even though most of the patients probably had extensive metabolizer genotypes.[21,22]

Recently, many studies have been reported in patients with cirrhosis and *H. pylori* infection.[27–35] It has been demonstrated that the eradication rate or *CYP2C19* polymorphisms are different in patients with cirrhosis and peptic ulcer disease, compared with those without cirrhosis.[30–32] However, our results must be interpreted within the context of the limitations of our study. First, we did not measure plasma rabeprazole levels and were therefore unable to correlate directly *H. pylori* infection and ulcer cure rates with plasma drug availability. Second, our sample size was small.[26] Therefore, our findings must be considered preliminary; further study is required in larger groups of patients with cirrhosis, and should include measurement of plasma rabeprazole concentrations. Furthermore, the clinical usefulness and cost-effectiveness of genotyping as a clinical tool in the management of *H. pylori*-associated gastrointestinal disease remain to be determined.[11] Thus, further study is needed to investigate the real correlation of *CYP2C19* genotype with eradication of *H. pylori* infection in patients with cirrhosis and peptic ulcer.

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