Effect of Omeprazole in One Patient with Peptic Ulcer

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Omeprazole, a proton pump inhibitor widely used in the treatment of reflux esophagitis and peptic ulcer, is metabolized by S-mephenytoin 4'-hydroxylase (CYP2C19), which is encoded on Cytochrome P450 in the liver. Genetic polymorphisms identified for CYP2C19 include the extensive metabolizer (EM), intermitted metabolizer (IM) and poor metabolizer (PM). We report a patient with reflux esophagitis and peptic ulcer who complained of persistent epigastric pain after taking omeprazole 40 mg per day for six weeks. The CYP2C19 genotype status for 2 mutations associated with the extensive metabolizer phenotype of this patient was determined by a polymerase chain reaction-restriction fragment length polymorphism method. We found that this patient exhibited the CYP2C19 extensive metabolizer polymorphism. However, the relationship between genetic polymorphisms of CYP2C19 and clinical usage of proton pump inhibitors is still unclear. **(Mid Taiwan J Med 2005;10:107-11)**

Key words

CYP2C19, genotype, proton pump inhibitors

INTRODUCTION

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 gastro-oesophageal reflux disease) [1-4]. Omeprazole, lansoprazole, and pantoprazole are metabolized by several CYPs, most prominently by CYP2C19 and CYP3A4 [5-8]. On the other hand, rabeprazole is metabolized mainly via a nonenzymatic reduction to a thioether compound with minor CYP2C19 involvement [9-13].

Hepatic drug oxidation is a major source of inter-individual variations in drug pharmacokinetics and therapeutic response. The discovery of polymorphic oxidative metabolism of S-mephenytoin 4'-hydroxylation via CYP2C19 has opened a new discipline in the study of drug metabolism [5,6].

As the metabolism of proton pump inhibitors (e.g. omeprazole) is mainly catalysed by CYP2C19 [3-5], genetic polymorphisms of CYP2C19 could be of clinical concern in the treatment of acid-related disease with proton pump inhibitors. In this study, we analyzed the relationship between the polymorphisms of CYP2C19 and patients with peptic ulcer diseases.

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CASE REPORT

A 47-year-old man had been complaining of abdominal pain for several weeks. The patient had no history of alcoholism, smoking, diabetes mellitus, hypertension or chronic liver disease. Physical examinations and biochemical laboratory data were normal. His medical history included a duodenal ulcer and reflux esophagitis. He also received omeprazole 40 mg per day for

Table. Genotyping revealed that this patient carried the CYP2C19 m1 (wt/wt) and CYP2C19 m2 (wt/wt) polymorphisms

Gene name	Wild type (wt/wt)	Homozygous (m1/m1)	Heterozygous (wt/m1)
CYP2C19*2 (CYP2C19 m1)	120 bp, 49 bp	169 bp	169 bp, 120 bp, 49 bp
CYP2C19*3 (CYP2C19 m2)	233 bp, 96 bp	329 bp	329 bp, 233 bp, 96 bp

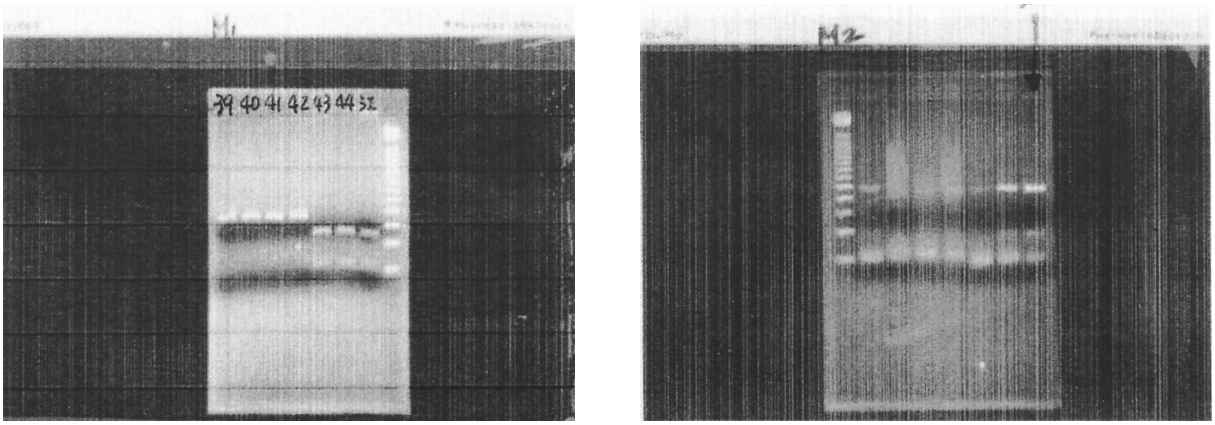

Figure. The products of wild-type CYP2C19 m3 (wt/wt) had two fragments of 120 bp and 49 bp. The products of homozygous CYP2C 19 m1 (m1/m1) had only one fragment of 169 bp. The products of heterozygous CYP2C19 m1 (wt/ml) had three fragments of 169 bp, 120 bp and 20 bp. The products of wild-type CYP2C19 m2 (wt/wt) had two fragments of 233 bp and 96 bp. The products of homozygous CYP2C19 m2 (m2/m2) had only one fragment of 329 bp. The products of heterozygous CYP2C19 m2 (wt/m2) had three fragments of 329 bp, 233 bp and 96 bp.

six months. Unfortunately, tests revealed that his liver function was abnormal after omeprazole therapy. Therefore, blood samples were obtained from this patient after he stopped omeprazole therapy, and CYP2C19 genotyping was performed [5,6].

DNA was extracted from the patient's leukocytes with a commercially available kit (Genomix, Talent, Trieste, Italy). Extracted genomic DNA was dissolved in distilled water (DNA solution). Genotyping procedures for identifying the CYP2C19 wt gene and the 2 mutated alleles, CYP2C19 (ml) and CYP2C19 (m2), were carried out by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with allele-specific primers, as described by de Morais et al [5,6]. We presumed that our patient had a second, unidentified, defect in the CYP2C19 gene. 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) containing 50 μM of dATP, dCTP, dGTP, and dTTP, 0.25 μM of PCR primers, 2.5 units of AmpliTaq DNA polymerase (Perkin Elmer Cetus), and 3.0 mM $MgCl_2$. The forward primer (5'-TATTATTATCTGTTAACTAATATGA-3') anneals to exon 3, 78 base pairs (bp) upstream from the exon 4/intron 3 junction, and the reverse primer (5'-ACTTCAGGGCTTGGTCAATA-3') anneals to intron 4, 88 bp downstream from the exon 4/intron 4 junction. Amplification was performed using a Perkin Elmer thermocycler, for 35 cycles consisting of denaturation at 94˚C for 1 min, annealing at 53˚C for 30 sec, and extension at 72˚C for 30 sec. An initial denaturation step at 94˚C for 5 min and a final extension step at 72˚C for 5 min were also performed. For sequencing, the PCR product was purified using Microcon (Amicon) columns, and an aliquot was used in the cycle sequencing reaction employing fluorescence-tagged dye terminators, the same forward primer used in the PCR, and an automated sequencer.

For detection of CYP2C19 (ml) in exon 5 and CYP2C19 (m2) in exon 4, genomic DNA (200 ng) was amplified in PCR buffer (50 μL)

containing 10 mmol/L Tris-hydrochloric acid (pH 8.3), 50 mmol/L potassium chloride, a 0.01% gelatin deoxyribonucleotide triphosphate (dNTP) mix (deoxyadenosine triphosphate (dATP), deoxycytidine triphosphate (dCTP), deoxyguanosine triphosphate (dGPT), and deoxythymidine triphosphate (dTTP); 200 μmol/L each as final concentration, Takara Shuzo Co, Ltd, Shiga, Japan)), 0.2 μmol/L concentrations of PCR primers, 1.25 units of AmpliTaq DNA polymerase (Hoffmann-La Roche, Ltd, Basel, Switzerland), and 1.5 mmol/L magnesium chloride. Amplification was carried out with an automatic thermal cycler (DNA Thermal Cycler PJ 2000, Perkin Elmer, Norwalk, Conn), for 40 cycles, consisting of denaturation at 94˚C for 1 min, annealing at 57˚C for 1 min, and extension at 72˚C for 2 min. An initial denaturation step at 94˚C for 5 min and a final extension step at 72˚C for 5 min were also performed. Restriction enzyme cleavage was conducted at 37˚C for 1 h after the addition of 25 units of MspI for CYP2C19 ml and 25 units of BamHI for CYP2C19 m2. The digested PCR products were analyzed on 3% agarose gels and stained with ethidium bromide. The genotyping test results for CYP2C19 m1 (CYP2C19*2) and CYP2C19 m2 (CYP2C19*3) are shown in Figure. As shown in Table, this patient carried CYP2C19 m1 (wt/wt) and CYP2C19 m2 (wt/wt), indicating that he carries the CYP2C19 extensive metabolizer (EM) phenotype.

DISCUSSION

Hepatic drug oxidation is a major cause of interindividual variations in drug 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, ageing, and environmental factors (smoking, alcohol, nutrition, and pollutants). As the metabolism of proton pump inhibitors is mainly catalysed by CYP2C19 and CYP3A4 [3,5,6], genetic polymorphisms of CYP2C19 could be of clinical concern in the treatment of acid-related diseases with proton pump inhibitors [2].

Oxidation shows considerable interethnic difference: approximately 2% to 6% of Caucasians and 1% of African-Americans have been identified as carrying the poor metabolizer (PM) phenotype, whereas the frequencies of PM phenotype have been reported to be 19% to 23% in Japanese, 15% in Chinese and 13% in Koreans [2,4]. Studies have shown that the primary defect in PM is a single base pair mutation in exon 5 of CYP2C19, resulting in an aberrant splice site [5,6]. This defect (referred to as CYP2C19 m1) is common in both Asian and Caucasian populations [2].

A second mutation, in exon 4 (CYP2C19 m2), appears to be present only in Asians [2]. According to the genotyping analysis of CYP2C19, PM consists of three genotypes (m1/m1, m2/m2, or m1/m2), while EM includes two genotypes, homozygous (wt/wt) and heterozygous (wt/m1 or wt/m2) EM [4]. With the presence of the additional mutant CYP2C19 m2 allele in Asian populations, less than 40% of Asians are homozygous for the wild-type allele. Therefore, the elimination of drugs metabolized by CYP2C19 (e.g. omeprazole, lansoprazole, pantoprazole, and diazepam) is much slower, and their plasma concentrations are greater in Asians than in Caucasians [3,5,6].

Since genetic oxidation status is a major determinant of the interindividual variations in plasma levels of drugs, the pharmacological effects elicited would be greater in those with the PM phenotype than those with the EM phenotype.

Therefore, individuals possessing the PM phenotype would be, in general, more prone to developing a dose-related adverse effect, while individuals possessing EM would be less likely to show a therapeutic response [8,9,10]. Considering the relationship between polymorphic oxidative activity and pharmacological response, genetic oxidative status may be an important etiological factor [4].

Some studies have shown that the plasma concentrations of omeprazole in PM carriers were much higher than those in individuals with EM [8]. Furthermore, the effect of omeprazole on intragastric pH was significantly affected by

CYP2C19 genotype status; therefore genotyping of CYP2C19 may be useful for an optimized or individualized omeprazole therapy [3,4]. Genetic polymorphisms involving the isoenzyme CYP2C19 significantly influence drug clearance and thus potentially have more impact on clinical efficacy of omeprazole in patients with reflux esophagitis. Unlike rabeprazole, omeprazole may inhibit CYP2C19 and thus have significant potential for pharmacokinetic drug-drug interactions, including diazepam, phenytoin, carbamazepine and warfarin [4,14,15].

We found that our patient's abnormal liver function test returned to normal after discontinuing omeprazole. We then gave this patient 20 mg rabeprazole per day for six weeks, which resulted in improvement in symptoms, including abdominal pain. In this respect, the balanced hepatic metabolism of rabeprazole, which involves both CYP-mediated and nonenzymatic hepatic reactions, appears to confer an advantage over omeprazole [5,6,13,14-16].

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Omeprazole 對十二指腸潰瘍患者之影響

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爲瞭解因十二指腸潰瘍必須服用質子幫浦抑制劑患者，引起肝功能異常後，其體內位於細胞內質網中群含血基質的Cytochrome P450 酵素系統，CYP2C19之基因多型性代謝情形，及其影響病患將來治療預後演變之臨床意義。故本研究病例即爲長期使用Omeprazole治療後之十二指腸潰瘍病患，且臨床上並發現到有肝功能異常現象，此病例之血漿中DNA測定發現其CYP2C19爲快速代謝者，故可能於一般治療劑量下Omeprazole於此病例血漿內濃度較低，導致臨床上療效不佳，但是否此類PPI藥物對此病例之CYP2C19基因型代謝系統有直接產生抑制破壞作用，而產生臨床上肝指數升高現象，則尚待更進一步研究探討。（中台灣醫誌 **2005;10:107-11**）

關鍵詞

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