

# Can *Helicobacter pylori* be eradicated with high-dose proton pump inhibitor in extensive metabolizers with the CYP2C19 genotypic polymorphism?

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**Abstract.** – Proton pump inhibitors (PPI) metabolism and pharmacokinetics are regulated by cytochrome P450 enzymes in the liver. Cytochrome P450 2C19 (CYP2C19) polymorphism plays an important role in the metabolism of PPIs. The three possible genotypes for CYP2C19 each has a distinct effect on the pharmacodynamics of PPIs. Homozygote extensive metabolizers (HomEM) are the most frequent genotype and have two wild-types (non-mutant) (\*1/\*1) alleles. HomEM is associated with increased enzyme activity, which increases the rate of PPI metabolism. Intra-gastric pH, which is required for eradication, is lowest in HomEM. In HomEMs, an insufficient increase in intra-gastric pH results in decreased anti-*Helicobacter pylori* (HP) efficacy of the antibiotics and, therefore, lower eradication rates. We determined whether the HP eradication rate would increase after high-dose PPI treatment of extensive PPI metabolizers who had been treated unsuccessfully with a standard PPI dose.

In our report, increasing the PPI dosage in patients with genotype polymorphisms may be effective on eradication rates. Eradication rates are directly affected by CYP2C19 polymorphisms, and eradication treatments should be planned considering such genotypic polymorphisms. Hence, CYP2C19 genotyping prior to treatment may facilitate determination of the optimum PPI dose to improve the therapeutic outcome. However, further researches are required to confirm this hypothesis.

Key Words:

CYP2C19, Homozygote extensive metabolizers, Proton pump inhibitors, High dose proton pump inhibitors.

## Introduction

The CYP2C19 genotypic polymorphism significantly affects the success of *Helicobacter pylori* (HP) eradication treatment<sup>1</sup>. All current treatment options for the eradication of *H. pylori* infection involve the combination of a proton pump inhibitor (PPI) and antibiotics<sup>2</sup>. PPIs are indispensable in the eradication of *H. pylori* infection, and the rationale for their use involves a number of potential mechanisms. PPI components with antisecretory properties increase gastric pH, therefore stabilizing acid-labile antibiotics in the stomach, and increase gastric luminal antibiotic concentrations<sup>3-5</sup>.

PPI metabolism and pharmacokinetics are regulated by cytochrome P450 enzymes in the liver, mainly S-mephenytoin-4-hydroxylase, which is encoded by CYP2C19<sup>6-7</sup>. The three possible genotypes for CYP2C19 each has a distinct effect on the pharmacodynamics of PPIs. Homozygote extensive metabolizers (HomEM) are the most frequent genotype and have two wild-types (non-mutant) (\*1/\*1) alleles. HomEM is associated with increased enzyme activity, which increases the rate of PPI metabolism. HP cannot be eradicated in HomEM due to the insufficient rise in intra-gastric pH and the low level of antibiotic bioavailability<sup>8</sup>. We determined whether the HP eradication rate would increase after high-dose PPI treatment of extensive PPI metabolizers who had been treated unsuccessfully with a standard PPI dose.

**Table I.** Eradication rates with different proton pump inhibitors (PPIs) in extensive metabolizers according to the CYP2C19 genotypic polymorphism.

<b>First-line therapy for extensive metabolizers according to the CYP2C19 genotypic polymorphism</b>	
Eradication rate	64.7% (101/156)
Eradication rate of the amoxicillin-clarithromycin-rabeprazole group	60 % (45/75)
Eradication rate of the amoxicillin-clarithromycin-pantoprazole group	69.1% (56/81)

**Table II.** Eradication rates with high-dose proton pump inhibitors (PPIs) in extensive metabolizers according to the CYP2C19 genotypic polymorphism (patients who failed the first-line treatment).

<b>Second therapy with high dose PPI in extensive metabolizers according to the CYP2C19 genotypic polymorphism</b>	
Eradication rate	80% (20/25)
Amoxicillin-clarithromycin-high dose rabeprazole	83.3% (10/12)
Amoxicillin-clarithromycin-high dose pantoprazole	76.9% (10/13)

Extensive PPI metabolizers, who had non-ulcerous dyspepsia and HP on an endoscopic evaluation and, according to an antrum-corpus biopsy, were still infected with HP after standard eradication treatment, were included in the study. In our previous work, 156 extensive PPI metabolizers were treated with a standard antibiotic dose, rabeprazole, and pantoprazole for 14 days to eradicate HP<sup>9</sup>. Among this group, the 25 patients who did not respond to the treatment were administered a high dose PPI as a second treatment. As in the first eradication treatment, 2 × 500 mg clarithromycin and 2 × 1 g amoxicillin were given as antibiotics. The rabeprazole dose was increased to 3 × 20 mg in the second treatment for the group taking 2 × 20 mg. The pantoprazole dose was increased to 3 × 40 mg for the group given 2 × 40 mg. HP antigen in the stool at the end of 12 weeks of treatment was used to determine treatment success. The HP eradication success rate after standard antibiotic treatment and a standard PPI dose was 64.7% (n = 101) for the 156 extensive metabolizers (Table I). HP eradication rates were not different in two groups. The 25 patients whose eradication treatments were unsuccessful were administered a second eradication treatment of high-dose PPI and a standard antibiotic dose for 3 months after the end of the previous treatment. The mean age of the patients given high-dose PPI and the standard antibiotic dose was 37 ± 13 (range, 18-61) years, and 68% (n = 17) were female. About 48% (n = 12) of the patients were given rabeprazole and 52% (n = 13) were given

pantoprazole. The eradication success rate of the group taking high-dose PPI (n = 25) was 80% (n = 20), and none of the patients stopped taking the drugs (Table II). We speculate that the higher eradication rate in those taking high-dose PPI was due to intragastric pH. Suppressing gastric acid secretion causes the intragastric pH to rise above 6, which favors amoxicillin activity in gastric juice<sup>10</sup>. The pH reached higher values during high-dose PPI treatment in extensive metabolizers. These findings suggest that extensive PPI metabolizers with failed eradication treatment should take a higher PPI dose before other treatment protocols are attempted. Increasing the PPI dosage in patients with genotype polymorphisms may be effective on eradication rates. Hence, CYP2C19 genotyping prior to treatment may facilitate determination of the optimum PPI dose to improve the therapeutic outcome.

#### Conflicts of interest

The authors declare no conflicts of interest.

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