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Review

Influence of CYP2C19 Pharmacogenetic Polymorphism on Proton Pump Inhibitor-based Therapies

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Summary: Proton pump inhibitors (PPIs), such as omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprazole, are mainly metabolized by CYP2C19 in the liver. There are genetically determined differences in the activity of this enzyme. The genotypes of CYP2C19 are classified into the three groups, rapid extensive metabolizer (RM), intermediate metabolizer (IM), and poor metabolizer (PM). The pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status. Plasma PPI levels and intragastric pHs during PPI treatment in the RM group are lowest, those in the IM group come next, and those in the PM group are highest of the three groups. These CYP2C19 genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs influence the cure rates for the gastro-esophageal reflux disease and *H. pylori* infection by PPI-based therapies. For the better PPI-based treatment, doses and dosing schemes of PPIs should be optimized based on CYP2C19 genotype status.

Key words: CYP2C19; *H. pylori*; proton pump inhibitor; GERD; pharmacogenomics

Introduction

Proton pump inhibitors (PPIs), such as omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprazole, are now widely used as the first-line acid inhibitors. They are absorbed in the small intestine and reach, *via* systemic circulation, to the gastric parietal cells, where they bind to the proton pump (H^+/K^+-ATPase) and disturb the function of proton pump, thereby resulting in a potent acid inhibition.[1)] The major indications of PPIs are acid-related diseases, such as peptic ulcer, gastro-esophageal reflux diseases (GERD), and Zollinger Ellison syndrome.[2–6)] PPIs are also used for the eradication of *H. pylori* with antibiotics such as amoxicillin and clarithromycin.[7–9)]

PPIs undergo the hepatic metabolism by the cytochrome P450 (CYP) system. The principal enzyme involved in the metabolism of PPIs is CYP2C19. CYP3A4 is also involved in the PPI metabolism.[10–14)] For example, omeprazole, a representative PPI, is mainly metabolized by CYP2C19 to 5-hydroxyomeprazole. 5-hydroxyomeprazole is then metabolized by CYP3A4 to 5-hydroxyomeprazole sulfone. Omeprazole is partially first metabolized by CYP3A4 to omeprazole sulfone, then metabolized to 5-hydroxyomeprazole sulfone by CYP2C19 (**Fig. 1**). There are interindividual differences in the activity of CYP2C19. Polymorphism of CYP2C19 influences pharmacokinetics and pharmacodynamics of PPIs. Herein, we describe and discuss about the effects of genetic polymorphism of CYP2C19 on the pharmacokinetics and pharmacodynamics of PPIs as well as on clinical outcomes of PPI-based therapies for gastroesophageal reflux disease and *H. pylori* infection.

Influence of CYP2C19 Polymorphism on Pharmacokinetics and Pharmacodynamics of PPIs

Genetic difference in the PPI metabolizing enzyme, CYP2C19: Interindividual difference in the activity of CYP2C19 was first characterized by the metabolism of

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Abbreviations used are: CYP2C19 = cytochrome P450 2C19, RM = rapid extensive metabolizer of CYP2C19, IM = intermediate metabolizer of CYP2C19, PM = poor metabolizer of CYP2C19, PPI = Proton pump inhibitor.

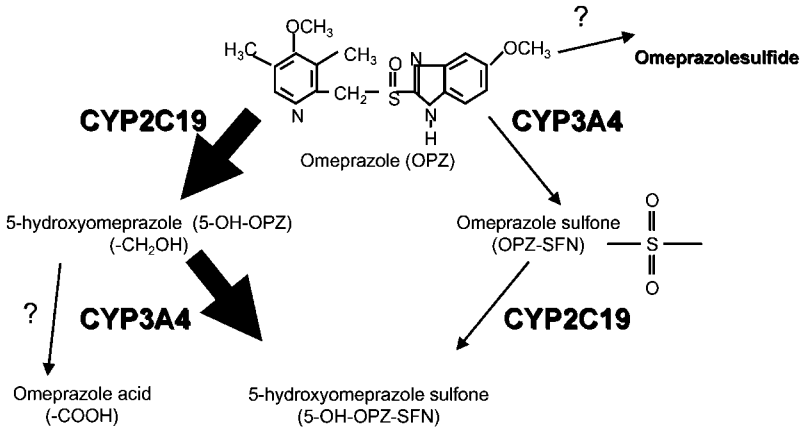

Fig. 1. Metabolic pathways of omeprazole (OPZ) in relation to cytochrome P450 (CYP) isoenzymes. Weight of arrows indicates the relative contribution of different enzyme pathways. OPZ is mainly metabolized by CYP2C19 to 5-hydroxyomeprazole (5-OH-OPZ), and then metabolized to 5-hydroxy-omeprazole sulfone (5-OH-OPZ-SFN) by CYP3A4. A small part of OPZ is first metabolized by CYP3A4 to omepraozole sulfone (OPZ-SFN), and then metabolized by CYP2C19 to 5-OH-OPZ-SFN. Question marks indicate that the enzyme involved in the pathways remains obscure.

mephenytoin; the *S*-enantiomer of mephenytoin undergoes hydroxidation through CYP2C19.[10,15,16] The phenotype of this enzyme was first classified into the two groups, extensive metabolizer (EM) and poor metabolizer (PM). After the analysis of genetics associated with the enzyme activity, polymorphism of this enzyme has been classified into the three genotype groups; the rapid extensive metabolizer (RM) group, the intermediate metabolizer (IM) group and the poor metabolizer PM group. Each genotype group corresponds to the homozygous extensive metabolizer (homEM), heterozygous extensive metabolizer (hetEM) and poor metabolizer (PM) in several previous reports.[17,18] In RMs, both of the alleles have no mutations and the enzyme can be generated from both of the non-mutated (wild type: wt) alleles (wt/wt). In IMs, the one allele has the mutation (m) in the coding region of CYP2C19. However, the other allele has no mutation and normal enzyme can be generated from this allele (wt/m). In PMs, both of the alleles have mutations in the CYP2C19 genes, and therefore, normal enzyme cannot be generated from any of the two mutated alleles, thereby resulting in the deficiency of the enzyme activity (m/m).

There are inter-ethnic differences in the frequencies of PMs of this enzyme: 2.5% in the white Americans, 2.0% in the African Americans, 3.5% in the white Europeans, 4.8% in Shona Zimbabweans, 19.8% in the Chinese-Han population, 13.4% in the Chinese-Bai population, 12.6% in the Korean population, and 18.0–22.5% in the Japanese population.[18–25] Various genetic mutations involved in the CYP2C19 polymorphism have been discovered from ethnically different populations (http://www.imm.ki.se/CYPalleles/cyp2c19.htm). However, the PM-related CYP2C19 polymorphism of Japanese people can be explained by the combination of two point mutations, *CYP2C19*2* of exon 5 and *CYP2C19*3* of exon 4.[24,26,27]

Effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of PPIs: When 20 mg of omeprazole is given as a single dose, plasma omeprazole concentrations differ among the three different CYP2C19 genotype (RM, IM, and PM) groups (**Fig. 2A**).[28] Plasma omeprazole levels in the PM group are sustained for a long time after dosing. Plasma levels of 5-hydroxyomeprazole, which is formed from omeprazole *via* CYP2C19, in the PM group are lower than those in the RM and IM groups (**Fig. 2C**). In PMs, the sulfoxidation of omeprazole is the main metabolic pathway and omeprazole sulfone cannot be metabolized to 5-hydroxyomeprazole sulfone by CYP2C19 in the PM group, because PMs lack CYP2C19. Therefore, plasma omeprazole sulfone levels are sustained for a long time after dosing in the PM group (**Fig. 2E**). Interestingly, hydroxylation of omeprazole in PMs is mediated mainly by CYP3A4.[29] The mean values for the areas under the plasma concentration-time curves (AUCs) of omeprazole in the PM group is about 13 times as high as that of the RM group (**Fig. 2B**). There are also significant differences in the two omeprazole metabolites, 5-hydroxyomeprazole and omeprazole sulfone levels among the three different CYP2C19 genotype groups (**Fig. 2D and 2F**, respectively).

When 20 mg of omeprazole is given as a single dose, the intragastric pH profile also differs among the three different genotype groups (**Fig. 3A**). The mean 24-hour intragastric pH level in the RM group is the lowest, that of the IM group comes next, and that in the PM group is highest (**Fig. 3B**). The acid inhibition achieved by 20 mg of omeprazole, the so-called standard dose, in the RM

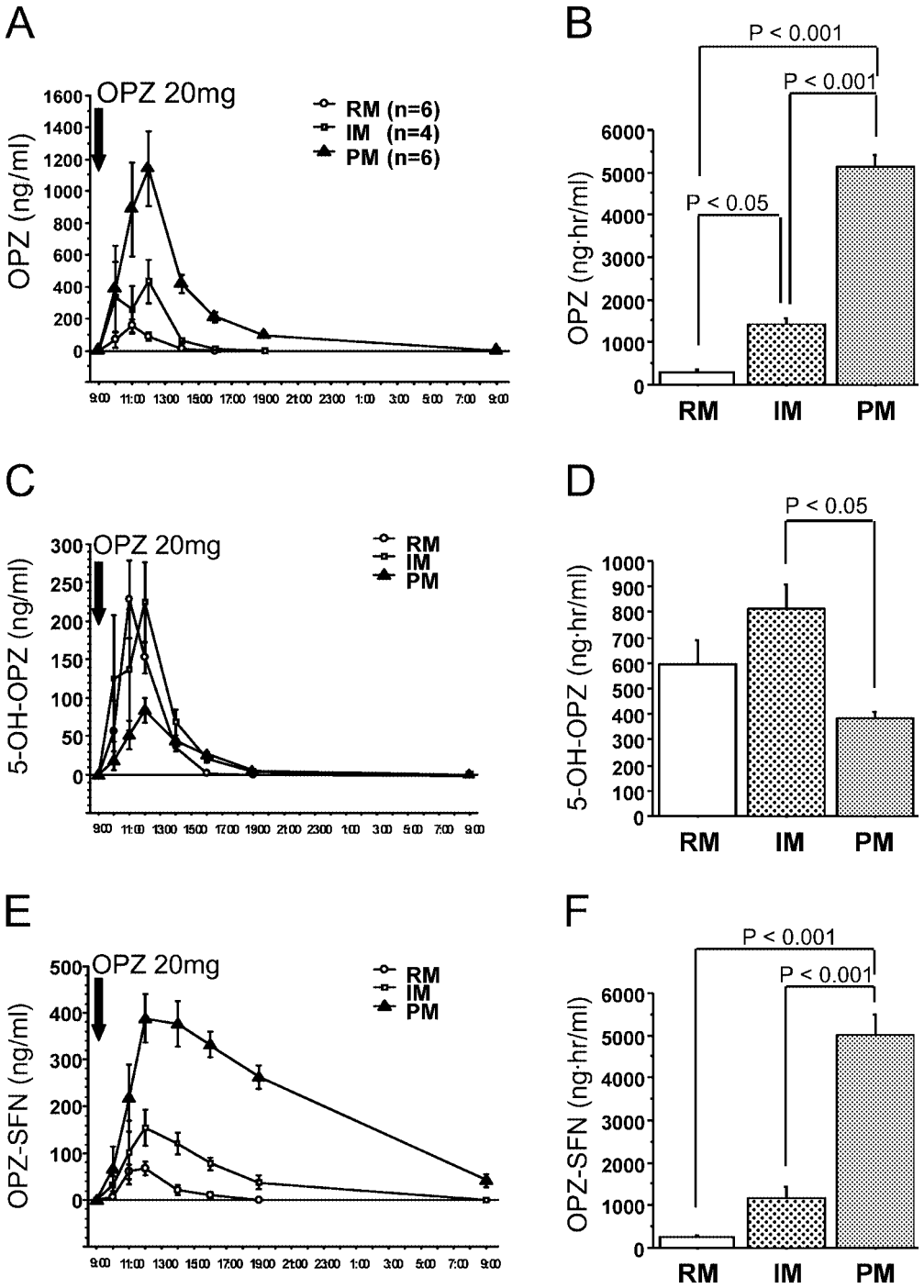

Fig. 2. Mean (±SE) plasma levels and areas under the plasma concentration-time curves (AUC) of omeprazole (OPZ) (A, B), 5-hydroxyomeprazole (5-OH-OPZ) (C, D), and omeprazole sulfone (OPZ-SFN) (E, F) as a function of CYP2C19 genotypes.
Abbreviations: RM = rapid extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer.

group seems to be therapeutically insufficient.[28,30]

Plasma concentration-time curves after the oral dosing of 20 mg of omeprazole, 30 mg of lansoprazole, and 20 mg of rabeprazole for 8 days also depend CYP2C19 genotype status. The mean values for the AUCs of omeprazole, lansoprazole, and rabeprazole in subjects with RM, IM or PM genotype of CYP2C19 are summarized in **Fig. 4**. Intragastric pH profiles after repeated dosings of 20 mg of omeprazole, 30 mg of lansoprazole, or 20 mg of rabeprazole for 8 days are also influenced by CYP2C19 genotype status (**Fig. 5**).[31–33] However, the difference in acid inhibitory effect of a

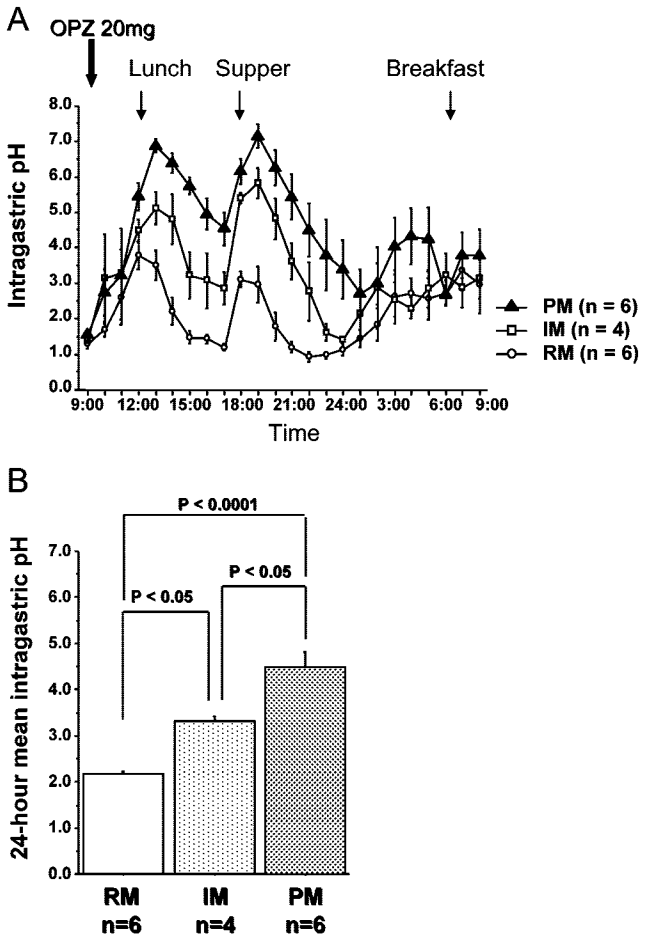

Fig. 3. Profiles of intragastric pH values (A) and the 24-hour mean intragastric pHs (B) as a function of CYP2C19 genotype status for 20 mg of omeprazole (OPZ) dosing.

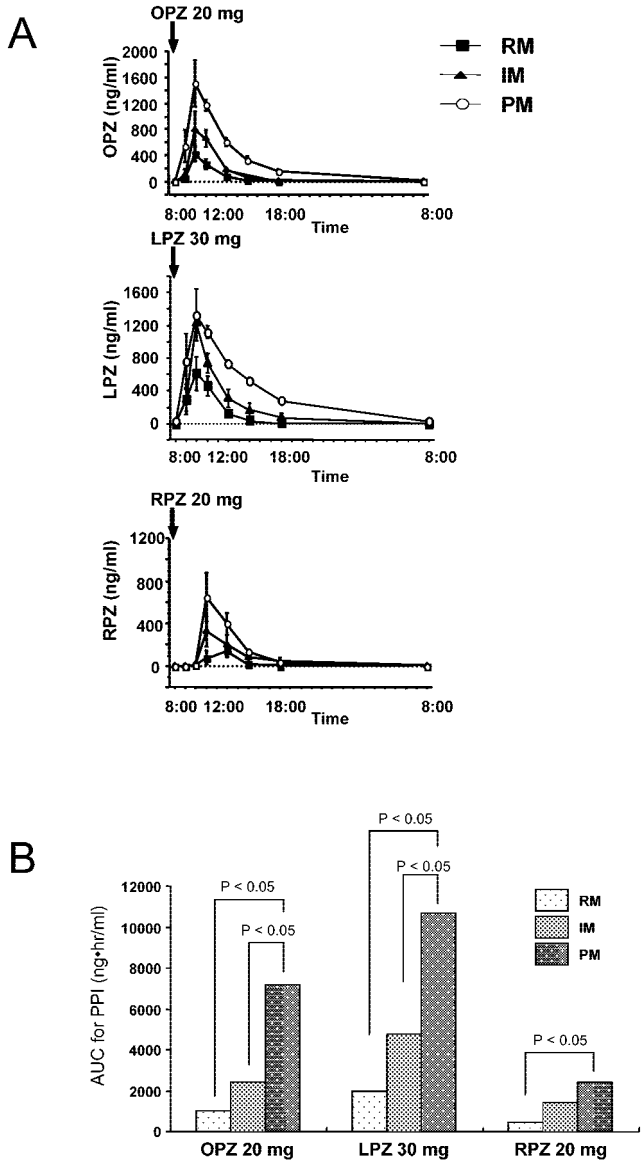

Fig. 4. Area under the plasma concentration time curves (AUCs) for omeprazole (OPZ), lansoprazole (LPZ), and rabeprazole (RPZ) as a function of CYP2C19 genotypes.

PPI among different CYP2C19 genotype status becomes smaller by the repeated dosing of a PPI. The differences in acid inhibition by a PPI among the different CYP2C19 genotype groups are considered to be due to different plasma concentrations among the different genotype groups.

Influence of CYP2C19 Polymorphism on GERD Treatment by a PPI

GERD represents a major indication of a PPI. The cure rates of GERD attained by PPIs are around 90%, while there seem some patients who are refractory to the usual standard dose of a PPI (e.g., 20 mg of omeprazole or 30 mg of lansoprazole).[34–36] Recently, one of the reasons for GERD refractory to the PPI treatment at the standard dose has been made clear to be associated with the metabolism of a PPI as discussed below.

When 30 mg of lansoprazole was dosed to GERD patients positive for mucosal breaks (Grades A–D in Los Angels Classification) for 8 weeks, cure rates of mucosal breaks based on endoscopy in the RM group was lowest, that in the IM group came next, and that in the PM group was highest (**Fig. 6**). Especially, the cure rate of grade C or D of GERD in patients with the RM genotype of CYP2C19 was dramatically low (1/6 = 16.7%, 95% CI: 0.4%–64.1%).[37] Plasma lansoprazole levels of GERD patients at 3 hours after the last dose depend on the CYP2C19 genotype status (**Fig. 7A**) and are also associated with cure rates mucosal breaks of GERD (**Fig. 7B**). Kawamura *et al.*[38] also reported that when 30 mg of lansoprazole was dosed to patients with erosive reflux esophagitis, the cure rate of mucosal breaks in the RM patients was lowest of the three different CYP2C19 genotype groups. CYP2C19

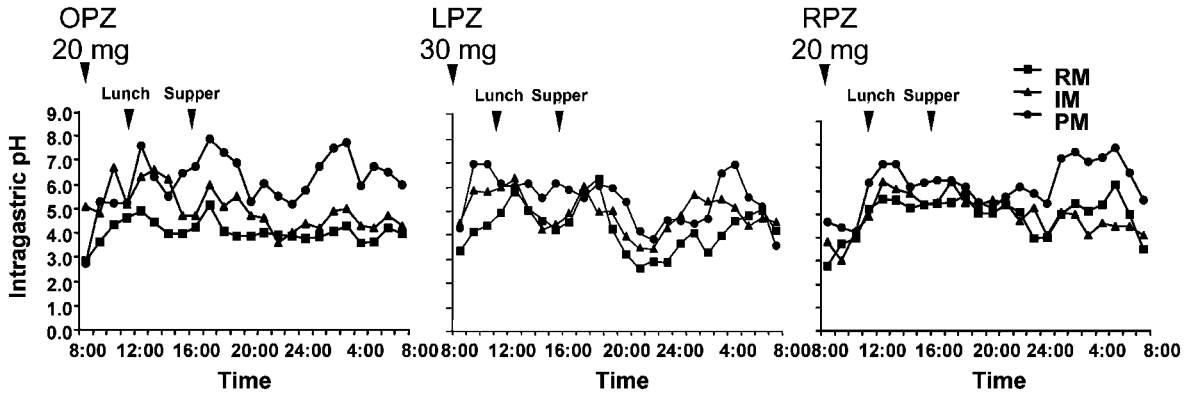

Fig. 5. Intragastric pH profiles for 20 mg of omeprazole (OPZ), 30 mg of lansoprazole (LPZ), or 20 mg of rabeprazole (RPZ) dosing for 8 days as a function of CYP2C19 genotype status.
See the legend of **Fig. 2** for the abbreviations.

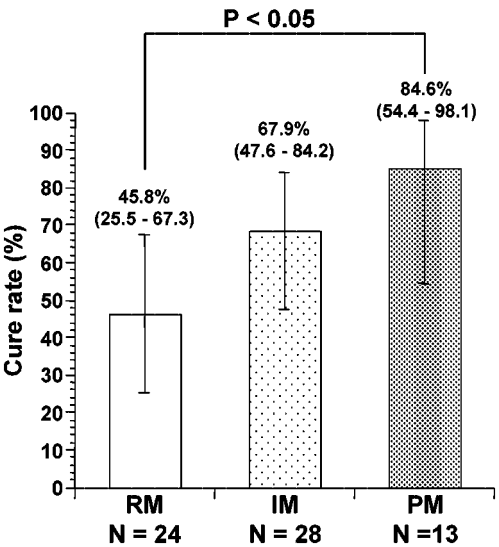

Fig. 6. Cure rates of GERD with a daily dose of 30 mg of lansoprazole for 8 weeks in the different CYP2C19 genotype groups. Bars indicate 95% confidence intervals (95% CI).

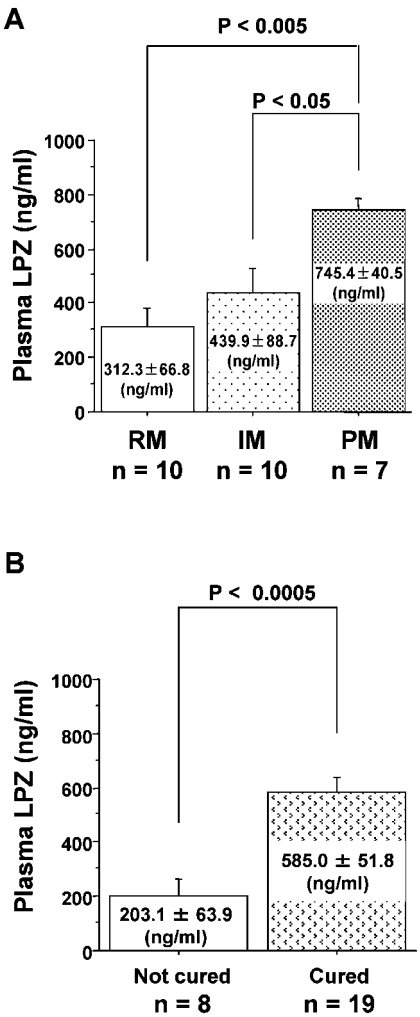

Fig. 7. The mean ± SE concentrations of plasma lansoprazole (LPZ) at 3 hours after the final 30 mg dose of LPZ in the different CYP2C19 genotype groups (A) and in the unsuccessfully or successfully treated groups (B).

genotype-dependent differences in the plasma lansoprazole levels are attributable to the different cure rates of GERD by lansoprazole at the standard dose.

Nocturnal acid breakthrough (NAB), which was defined as an intragastric pH lower than 4.0 lasting for more than one hour during the overnight period, is now considered as one of the factors associated with the success or failure of treatment of GERD with PPIs.[39-42] Interestingly, the frequency of NAB depends on the CYP2C19 genotype status. NAB occurs more frequently in RM patients than in patients with the IM or PM genotype of CYP2C19,[32,33,43] which could give an explaination for the low cure rate of GERD in the RM patients.[37,38]

On the basis of the above discussion, an increased dose of a PPI is recommended for the EM (particularly

RM) GERD patients who are refractory to the treatment with a usual standard dose of a PPI. In fact, a usual dose of a PPI, such as 20 mg of omeprazole daily, was reported to be therapeutically insufficient for some patients in western countries, whereas an increased dose of omeprazole, up to 80 mg daily, successfully treated such patients,[44] in spite of the fact that the majority of Westerners have the RM genotype of CYP2C19.[45] A more frequent daily dosing of a PPI (e.g., lansopraozole 30 mg or rabeprazole 20 mg four times a day) can achieve a sufficient acid suppression (i.e., intragastric pH around 7) in the RM genotype group as noted above.[33,43] Therefore, a frequent dosing of a PPI might be one of the therapeutic strategies for the treatment of GERD refractory to the usual dose of a PPI in patients with the RM genotype of CYP2C19.

Possible Adverse Events by Long-term Treatment with a PPI with Reference to CYP2C19 Polymorphism

GERD can be controlled by a PPI treatment, but cannot be cured essentially, because most GERDs soon or later recur by stopping the PPI-treatment. Therefore, the maintenance therapy with a PPI for a long time is required and recommended for the control of GERD. However, the long-term effect of a PPI on human body has not been fully studied.

Although the long-term treatment with omeprazole was reported to induce the carcinoid tumors in rodent, the effect of long-term acid inhibition by a PPI on the hyperplasia of enterochromaffin-like (ECL) cells in human has been controversial.[46–49] Sagar *et al.*[50] studied the effect of 1-year treatment with 20 mg of omepraozle on the serum gastrin, and found that serum gastrin levels did not increase in comparison with those after the initial doing of omeprazole in RMs, but increased in IMs. They also studied the serum chromogranin A levels, the indicator of hyperplasia of ECL cells, in GERD patients treated with omeprazole for 1 year. They found that there was no increase in serum chromogranin A levels after 1-year treatment in RMs, but that the significant increase was observed in IMs. Previously, the risk of hyperplasia of ECL cells by long-term treatment with a PPI was reported to be low in humans,[47] which seems to be due to the high incidence of RMs in the study subjects from Caucasians.[45] Therefore, we may have to pay an attention to IMs and PMs who undergo the long-term treatment with a PPI for the possible risk of hyperplasia of ECL cells, which is related to the developing carcinoid tumor.

Vitamin B12 is released from meal by digestion with gastric acid and absorbed in the ileum with support of intrinsic factor secreted from parietal cells. Therefore, the absorption of vitamin B12 is considered to be decreased by acid inhibition. The long-term treatment with 40–60 mg of omeprazole was reported to cause megaloblastic anemia in a GERD patient becaused of decreased absorption of vitamin B12.[51] Sagar *et al.*[52] also reported that serum vitamin B12 levels decreased after 1-year treatment with omeprazole in IMs and PMs, but not in RMs.

Kuipers *et al.*[53,54] reported that GERD patients with *H. pylori* infection who are treated with omeprazole for a long time are at an increased risk of atrophic gastritis, which is thought to be a precursor of gastric cancer.[55–57] Progression of gastric atrophy also leads to intrinsic factor deficit and decreased acid secretion with consequent failure to absorb vitamin B12, resulting in the increased risk of megaloblastic anemia. Sagar *et al.*[50] also studied the serum pepsinogen I levels, as a marker of gastric atrophy, before and 1 year after treament with omeprazole in GERD patients and found that the mean serum pepsinogen I level in IMs was significantly decreased after 1 year treatment in comparison with RMs. They found that decrease in serum pepsinogen I levels was more evident in patients infected with *H. pylori*. Therefore, patients with IM or possibly with PM genotype of CYP2C19 are at an increased risk of atrophic gastritis by a long term treatment with a PPI, particularly when *H. pylori* infection exists. Accordingly, the eradication of *H. pylori* is strongly recommended for the *H. pylori*-positive patients (particularly, IMs and/or PMs) who undergo the long-term treatment with a PPI.

Influence of CYP2C19 Polymorphism on PPI-based Eradication Therapy of *H. pylori*

Eradication of *H. pylori* is now an important treatment strategy for the cure of a variety of upper gastrointestinal disorders, such as peptic ulcer and mucosa-associated lymphoid tissue lymphoma. Current regimens for the eradication of *H. pylori* consist of a PPI plus one or two of antibacterial agents, such as amoxicillin, clarithromycin, and metronidazole.

A PPI is one of the key drugs in *H. pylori* eradication therapy because of the following reasons: first, a PPI makes antibiotics more stable and bioavailable in the stomach by raising intragastric pH to neutral levels.[58] Second, neutralization of intragastric pH levels by a PPI allows *H. pylori* to reach at the growth phase and thus becomes more sensitive to antibiotics, such as amoxicillin.[59,60] Third, suppression of acid secretion by a PPI increases the concentration of an antibiotic, such as amoxicillin, in the stomach.[61] Fourth, PPIs per se have an anti-*H. pylori* effect.[62] Therefore, a PPI is indispensable in *H. pylori* eradication therapy. As a matter of fact, the cure rates achieved by treatment with two anti-bacterial agents (amoxicillin plus clarithromycin or clarithromycin plus metronidazole) without a PPI were significantly lower than those achieved by the treatment with the same two anti-bacterial agents plus

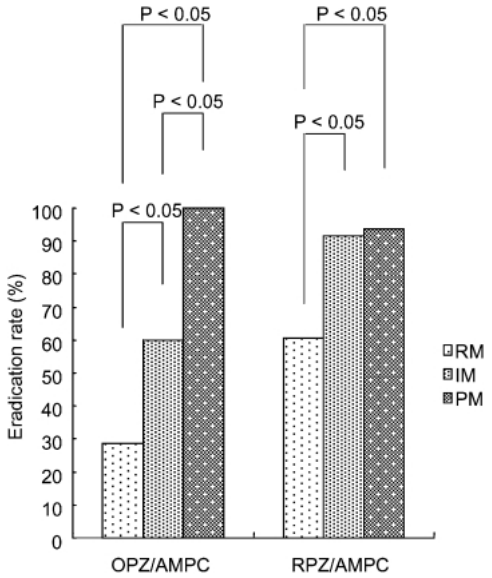

Fig. 8. Cure rates for *H. pylori* infection by dual therapy with 20 mg of omeprazole plus 2000 mg of amoxicillin for 2 weeks (OPZ/AMPC) and the dual therapy with 20 mg of rabeprazole plus 1500 mg of amoxicillin for 2 weeks (RPZ/AMPC) as a function of the CYP2C19 genotype groups.
See the legend of **Fig. 2** for the abbreviations.

omeprazole, a representative protoptype PPI.[63]

Dual PPI/amoxicillin eradication therapy for *H. pylori* infection in relation to CYP2C19 polymorphism: The eradication rates for *H. pylori* by dual omeprazole/amoxicillin (omeprazole 20 mg once daily plus amoxicillin 500 mg 4-times daily for 2 weeks) are around 30% in the RMs, 60% in the IMs, and 100% in the PMs (**Fig. 8**).[64] Differences in pharmacokinetics and pharmacodynamics as an acid inhibitor of omeprazole among the different CYP2C19 genotype groups are assumed to result in the different eradication rates among the correspondent genotype groups. Similarly, Aoyama *et al*.[65] reported that eradication rates by dual omeprazole/amoxicillin therapy (omeprazole 40 mg plus amoxicillin 2000 mg daily for 1 week) were 33% in the RMs, 30% in the IMs and 100% in the PMs.

The eradication rates by dual rabeprazole/amoxicillin (rabeprazole 10 mg twice daily plus amoxicillin 500 mg 3-times daily for 2 weeks) seems to be better than the dual omeprazole/amoxicillin therapy noted above. The total averaged cure rate achieved by a dual rabeprazole/amoxicillin therapy was around 80%. The acid inhibitory effect of rabeprazole is so potent[66] that a sufficient acid inhibition can be achieved by rabeprazole at the usual standard dose in RMs,[31,67] and therefore, high cure rates for *H. pylori* infection were achieved by dual rabeprazole/amoxicillin therapy. However, the cure rates by this regimen were also affected by the different CYP2C19 genotype status (**Fig. 8**).[68]

Interestingly, the cure rate achieved by the dual rabeprazole/amoxicillin therapy in the IM plus PM groups (92.2%)[68] was so high as that achieved by current PPI-based triple therapies.[7,63,69–71] However, such current triple therapies have problems of bacterial resistance to clarithromycin or metronidazole.[72–74] Metronidazole has also been reported to exhibit a possible risk of later development of lung cancer.[75] Because 65%–70% of Asians and 20%–25% of Caucasian individuals are IM or PM genotypes or phenotypes of CYP2C19[45,76–78] and there are quite few amoxicillin-resistant strains of *H. pylori*,[79] the dual rabeprazole/amoxicillin therapy would yield, on a theoretical basis, a better than 90% success rate in curing *H. pylori* infection in 65%–70% of Asian and 20%–25% of Caucasian patients, without the second anti-bacterial agent, such as clarithromycin or metronidazole. For the RM patients, a dual high-dose rabeprazole (10 mg, 4 times daily) plus amoxicillin (500 mg, 4 times daily) therapy used as a second-line therapy in our previous study is sufficiently effective.[68,80] Therefore, if patients' CYP2C19 genotype status is determined before the treatment, an individualized optimal treatment schedule (e.g., rabeprazole 10 mg/day plus amoxicillin 500 mg 4 times daily for RMs, and rabeprazole 10 mg twice daily plus amoxicillin 500 mg 3 times for IMs and PMs) can be performed and the cure rate achieved by the initial treatment is expected to become higher without use of clarithromycin or metronidazole. Therefore, the genotyping test of CYP2C19 is assumed to be a clinically useful tool for an optimal treatment selection of a PPI-based *H. pylori* eradication therapy.

Triple PPI/amoxicillin/clarithromycin therapy for *H. pylori* infection in relation to CYP2C19 polymorphism:

a. Interaction between PPI and clarithromycin: One of the current regimens for eradication of *H. pylori* is triple PPI/amoxicillin/clarithromycin therapy.[8] However, there exists a possible drug-drug interaction between PPIs and clarithromycin. Clarithromycin is not only metabolized by CYP3A4, but also a potent inhibitor of CYP3A4. CYP3A4 is involved in the sulfoxidation of PPIs.[81] Clarithromycin also inhibits the activity of CYP2C19 a little.[82] Therefore, when a PPI and clarithromycin are co-administered, a drug-drug interaction between a PPI and clarithromycin can occur, resulting in the observation that plasma omeprazole levels are increased by co-administration with clarithromycin in each of the different CYP2C19 genotype groups (**Fig. 9**). Inhibition of CYP3A4 by clarithromycin lets the PMs to lose the two main metabolic pathways of omeprazole, CYP2C19 and CYP3A4, leading to extremely high plasma omeprazole levels in PMs.[29] Ushiyama *et al*.[83] have also demonstrated that

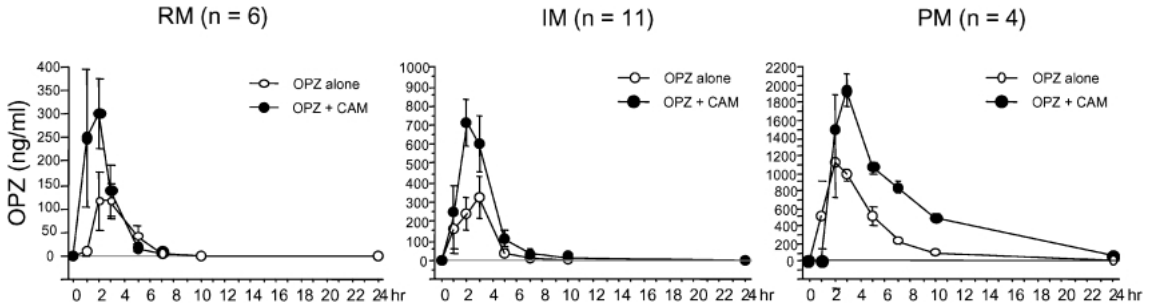

Fig. 9. Mean (±SE) plasma levels of omeprazole (OPZ) in the RM, IM, and PM groups with and without clarithromycin (CAM). See the legend of **Fig. 2** for the abbreviations.

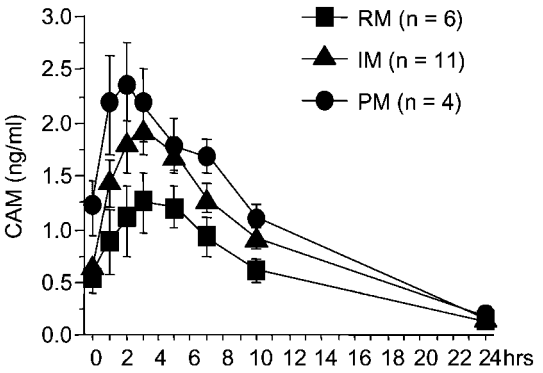

Fig. 10. Mean (±SE) plasma concentration time-curves of clarithromycin (CAM) in the three different genotype groups. See the legend of **Fig. 2** for the abbreviations.

clarithromycin increases plasma lansoprazole levels by inhibiting the CYP3A4 activity in patients who undergo the triple lansoprazole/amoxicillin/clarithromycin therapy. Saito *et al*.[84] have also reported the similar findings. These results indicate that the drug-drug interaction between clarithromycin and a PPI may underlie the high cure rate for the eradication of *H. pylori* obtained by a triple PPI/amoxicillin/clarithromycin therapy. Plasma clarithromycin levels also differ among the different CYP2C19 genotype groups **(Fig. 10)**,[29] which is assumed to influence eradication rates by regimens including a PPI and clarithromycin.

b. Influence of CYP2C19 polymorphism on triple PPI/amoxicillin/clarithromycin therapy for H. pylori infection at the usual dose: Differences in plasma clarithromycin and PPI levels among the different CYP2C19 genotype groups result in different cure rates for *H. pylori* infection among the respective different CYP2C19 genotype groups. In our previous study,[85] eradication rates for *H. pylori* infection by a triple therapy with daily doses of omeprazole 40 mg or lansoprazole 60 mg, amoxicillin 1500 mg, and clarithromycin 600 mg for 1 week were 72.7% in RMs, 92.1% in IMs, and 97.8% in PMs **(Fig. 11)**. The incidence of the RM genotype was higher in the group without eradication, while the incidence of the PM genotype in patients without eradication was very low **(Fig. 12A)**. Aoyama *et al*.[65] have reported that cure rates by triple omeprazole/amoxicillin/clarithromycin therapy were 81% in RMs, 94.5% in IMs, and 100% in PMs. Tanigawara *et al*.[86] have also reported the similar results. Dojo *et al*.[87] have reported that cure rates by triple omeprazole/amoxicillin/clarithromycin therapy were 73.3% in RMs, 86.1% in IMs, and 85.0% in PMs (not statistically significant). Taken together, these reports demonstrate that one of the reasons for the eradication failure of *H. pylori* by a triple PPI/amoxicillin/clarithromycin therapies is considered due to the insufficient dose of a PPI (omeprazole or lansoprazole) in RMs. In other words, the RM genotype of CYP2C19 is one of the possible causes for the eradication failure of *H. pylori* infection by a triple PPI/amoxicillin/clarithromycin therapy as well as by a dual PPI/amoxicillin therapy.

Another important factor associated with success or failure of *H. pylori* eradication by a triple PPI/amoxicillin/clarithromycin therapy is bacterial resistance to clarithromycin. More than half of patients who had failed in eradication by a triple PPI/amoxicillin/clarithromycin therapy were infected with the clarithromycin-resistant strain of *H. pylori* **(Fig. 12B)**. Bacterial resistance to clarithromycin is caused by mutation in 23S rRNA, which can be detected by molecular analyses.[88–91] In our previous report,[85] eradication rates in RM, IM and PM patients infected with clarithromycin-sensitive strain of *H. pylori* were relatively high, whereas the eradication rate in RM patients infected with clarithromycin-resistant strain of *H. pylori* was dramatically low (7.1%). Therefore, we conclude that the major factors associated with success or failure of the eradication of *H. pylori* by a triple PPI/amoxicillin/clarithromycin therapy are not only CYP2C19 (particularly RM) genotype status, but also bacterial resistance to clarithromycin.

Second line therapy for eradication failure by PPI/

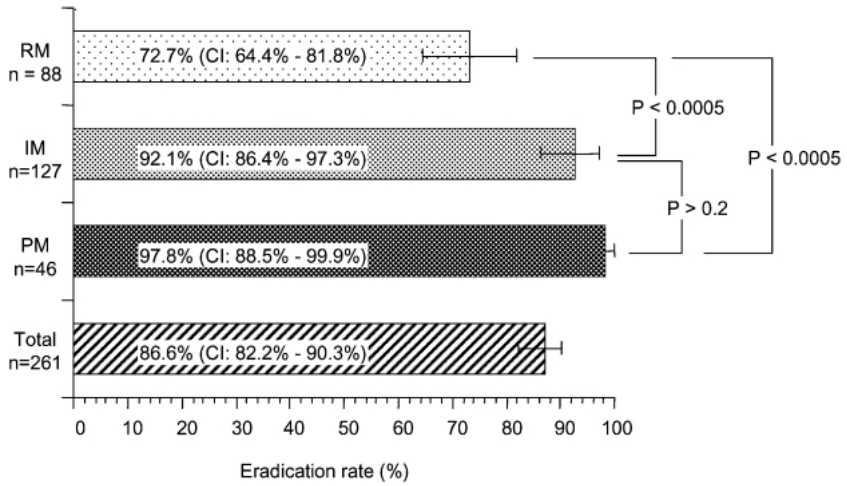

Fig. 11. *H. pylori* eradication rates achieved by the triple PPI/amoxicillin/clarithromycin therapy in the total and for the different CYP2C19 genotype groups. Bars indicates 95% confidence intervals (95% CI). See the legend of **Fig. 2** for the abbreviations.

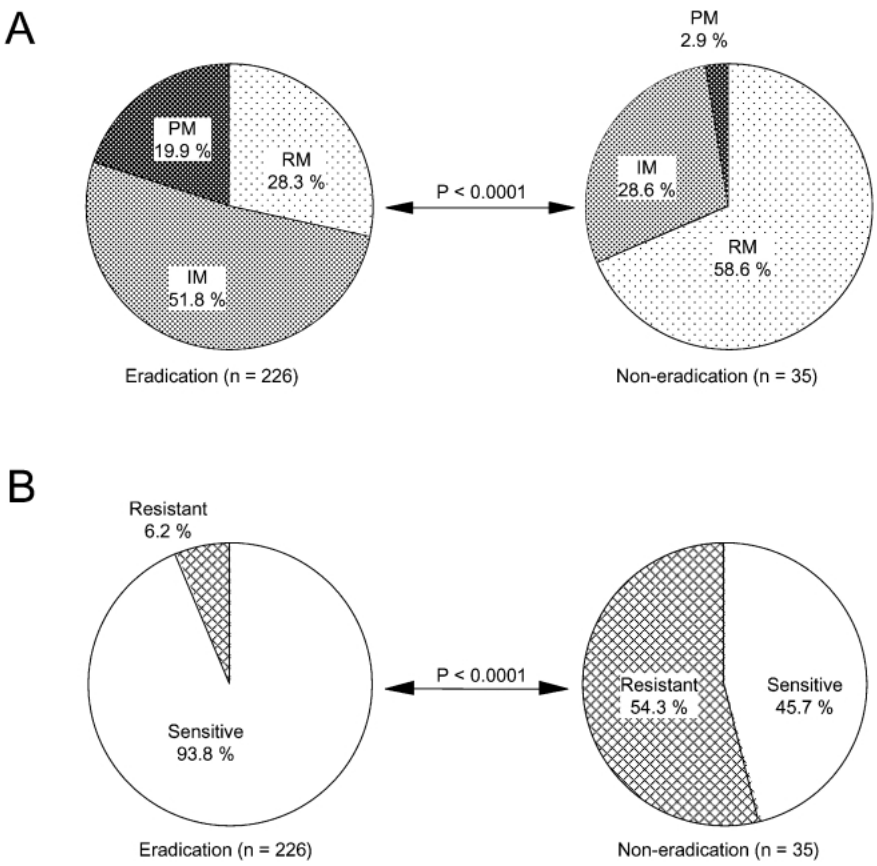

Fig. 12. A. Frequencies of CYP2C19 genotypes in patients with eradication and non-eradication of *H. pylori* infection by triple PPI/amoxicillin/clarithromycin therapy.
B. Frequencies of clarithromycin-sensitive and -resistant strains of *H. pylori* in patients with and without eradication of *H. pylori* infection achieved with triple PPI/amoxicillin/clarithromycin therapy. See the legend of **Fig. 2** for the abbreviations.

Table 1. Cure rates of *H. pylori* infection by treatment with high doses of a PPI plus amoxicillin

Regimen	Cure rates % (PP)	Reference
OPZ 40 mg 3 times daily + AMPC 750 mg three times daily for 2 weeks	91%	(92)
OPZ 40 mg 4 times daily + AMPC 750 mg 4 times daily for 2 weeks	83.3%	(93)
LPZ 30 mg 4 times daily + AMPC 500 mg 4 times daily for 2 weeks	96.7%	(85)
RPZ 10 mg 4 times daily + AMPC 500 mg 4 times daily for 2 weeks	100.0%	(68, 80)

PP = per protocol analysis, OPZ = omeprazole, LPZ = lansoprazole, RPZ = rabeprazole

amoxicillin/clarithromycin therapy at the usual dose: The majority of patients who fail in the eradication of *H. pylori* infection by PPI/amoxicillin/clarithromycin therapy at the usual doses (i.e., those of omeprazole and lansoprazole, as discussed above) have the RM genotype of CYP2C19 and/or are infected with a clarithromycin-resistant strain of *H. pylori*. However, the amoxicillin-resistant strain of *H. pylori* is quite rare,[79] and therefore, treatment with an increased dose of one of PPIs and amoxicillin is expected to succeed in the eradication of *H. pylori* in patients who have had therapeutic failure by the initial treatment with the triple therapy with a PPI, amoxicillin, and clarithromycin at the usual dose. Bayerdorffer *et al*.[92] reported that around 90% of the eradication rate could be achieved by the dual therapy with 120 mg of omeprazole plus 2.25 g of amoxicillin daily for 2 weeks, indicating that sufficient cure rates for *H. pylori* infection can be obtained by the dual therapy with a PPI and amoxicillin at a high dose. We have chosen the dual therapy with high doses of PPI plus amoxicillin for the retreatment strategy, where lansoprazole 30 mg or rabeprazole 10 mg plus 500 mg of amoxicillin were dosed 4 times daily for 2 weeks and sufficient cure rates higher than 90% have been obtained,[68,80,85] because 4 times daily dosing of a PPI can yield a sufficient acid inhibition (intragastric pH is kept at around 7 throughout the 24-hour period of the day),[33,43] where amoxicillin is supposed to be more stable and bioavailable under a higher intragastric pH (i.e., around 7.0) and the bactericidal effect of amoxicillin is expected to be fully enhanced. Miehlke *et al*.[93] also reported that the dual therapy with very high doses of omeprazole and amoxicillin was as effective as a quadruple therapy for the second-line regimen. The reported cure rates of *H. pylori* infection by treatment with high doses of a PPI plus amoxicillin are summarized in **Table 1**.

The important issue in the therapy with high doses of a PPI and amoxicillin is the dosing scheme. Isomoto

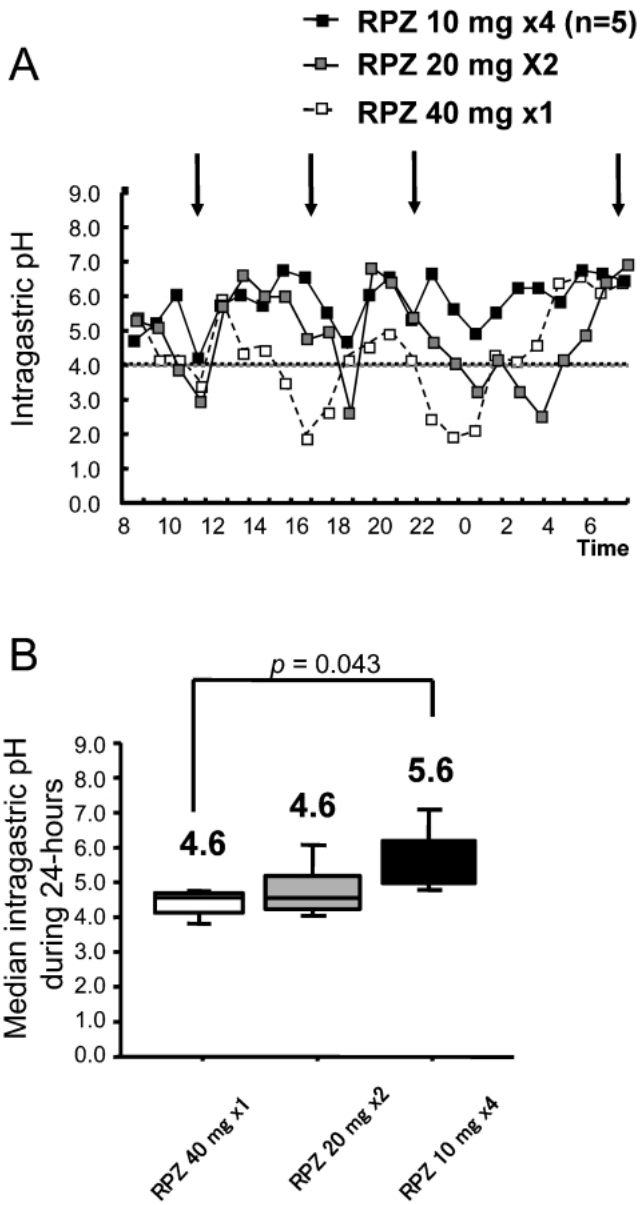

Fig. 13. Intragastric pH profiles (A) and the medians of 24-hour intragastric pHs (B) in RMs of CYP2C19 when dosed with 40 mg of rabeprazole once daily, 20 mg of rabeprazole twice daily, and 10 mg of rabeprazole 4 times daily.

et al.[94] have reported that the cure rate achieved by the twice daily dosing of 20 mg of rabeprazole and 1000 mg of amoxicillin for 2 weeks was less than 60%. The total doses of rabeprazole and amoxicillin in this study was the same as ours, but the dosing schemes were completely different between each other. Differences in acid inhibitory effects between rabeprazole 20 mg twice daily and rabeprazole 10 mg 4 times daily are significant. It has been demonstrated that the dosing of 10 mg rabeprazole 4 times daily is necessary for the achievement of sufficient acid inhibition in RMs and that sufficient acid inhibition cannot be attained by 20 mg of

rabeprazole twice daily (**Fig. 13**).[43] Moreover, antibiotics with the beta-lactam ring, such as amoxiciilin, has little post-antibiotic effect on the gram-negative rods.[95] Their anti-bacterial effect depends on the time above MIC, but not on the AUC or Cmax of antibiotics. Therefore, the twice-daily dosing of 1000 mg of amoxicillin is theoretically inappropriate and wrong from the point of a view of pharmacology of antibiotics. The total dose of 2000 mg of amoxicillin should be dosed as 500 mg 4 times daily, but not 1000 mg twice daily. *H. pylori* eradication therapy definitively requires many aspects of clinical pharmacology including not only pharmacogenetics but also pharmacokinetics and pharmacodynamics of drugs when developing an academic-based treatment strategy.

The clinical pharmacological basis for *H. pylori* eradication is summarized as follows: first, select an antibacterial agent to which *H. pylori* is sensitive. Second, make the environmental condition in the stomach more optimal under which the selected antibacterial agent becomes more stable and bioavailable, by co-administering the sufficient dose of a PPI chosen in relation to the individual CYP2C19 genotype status. The dosing scheme of antibiotics is also important, especially in the use of amoxicillin. The treatment plan individualized on the basis of above-mentioned items is expected to increase the eradication rate by the initial therapy.

Conclusion

Not only pharmacokinetics and pharmacodynamics of a PPI, but also clinical outcomes by PPI-based therapy are affected by a CYP2C19 genotype status or pharmacogenomics. PPIs are now the first choice for acid inhibition. Moreover, a PPI is dosed for a long time for GERD patients. Clinical effects of PPIs depend on the CYP2C19 genotype status of patient as discussed in this review. Therefore, this genotyping test is a useful clinical tool for the optimal PPI treatment. The cost-effectiveness of this genotyping test needs to be verified in a future study.

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