LEADING ARTICLE

Mol Diagn Ther 2012; 16 (4): 223-234
1177-1062/12/0004-0223/$49.95/0

Individualized Therapy for Gastroesophageal Reflux Disease

Potential Impact of Pharmacogenetic Testing based on *CYP2C19*

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Abstract

The main therapeutic agent for gastroesophageal reflux disease (GERD) is a proton pump inhibitor (PPI). Plasma levels and the acid inhibitory effect of PPIs depend on the activity of cytochrome P450 (CYP) 2C19, which is polymorphic. Genotypes of *CYP2C19* are classified into three groups: rapid metabolizers (RMs: *1/*1), intermediate metabolizers (IMs: *1/*X), and poor metabolizers (PMs: *X/*X), where *1 and X represent the wild type and the mutant allele, respectively. RMs include ultra-rapid metabolizers, who possess the *CYP2C19**17 allele. The pharmacokinetics and pharmacodynamics of PPIs differ among different *CYP2C19* genotype groups. Plasma PPI levels and intragastric pH values during PPI treatment are lowest in the RM group, intermediate in the IM group, and highest in the PM group. These *CYP2C19*-genotype-dependent differences in the pharmacokinetics and pharmacodynamics of PPIs influence the healing and recurrence of GERD during PPI treatment, suggesting the need for *CYP2C19* genotype-based tailored therapy for GERD. *CYP2C19* pharmacogenetics should be taken into consideration for the personalization of PPI-based therapy. However, the clinical usefulness of *CYP2C19* genotype testing in GERD therapy should be verified in clinical studies.

1. Introduction

Gastroesophageal reflux disease (GERD) is a common disorder estimated to affect approximately 35–40% of the adult population in the Western world.[1] GERD now represents a major indication for proton pump inhibitors (PPIs). However, there seem to be some patients who do not respond to the usual daily dose of a PPI (e.g. omeprazole 20 mg or lansoprazole 30 mg).[2,3] Therefore, it is of clinical importance to develop an optimal therapeutic strategy for GERD patients who are refractory to a PPI at the standard dose.

PPIs are substituted benzimidazoles and are mainly metabolized by the cytochrome P450 (CYP) system in the liver. The principal enzyme involved in the metabolism of PPIs is CYP2C19, though CYP3A4 is also involved in PPI metabolism.[4-8] There are interindividual differences in the activity of CYP2C19, and the pharmacokinetics and pharmacodynamics of PPIs are influenced by *CYP2C19* genetic polymorphism.

Herein, we describe and discuss the influence of *CYP2C19* genetic polymorphism on the pharmacokinetics and pharmacodynamics of PPIs and on clinical outcomes of PPI-based therapies for GERD. We also discuss the prospects for *CYP2C19* genotype-based personalized treatment of GERD.

2. Effects of CYP2C19 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Proton Pump Inhibitors (PPIs)

2.1 Genetic Differences in the PPI-Metabolizing Enzyme CYP2C19

CYP2C19 is involved in the first step of metabolism of all PPIs (figure 1).[9,10] Because the metabolites of PPIs (such as 5-hydroxyomeprazole and omeprazole sulfone) have no acid-inhibitory effect, the therapeutic effect depends on plasma levels of the PPIs, which are determined by the activity of

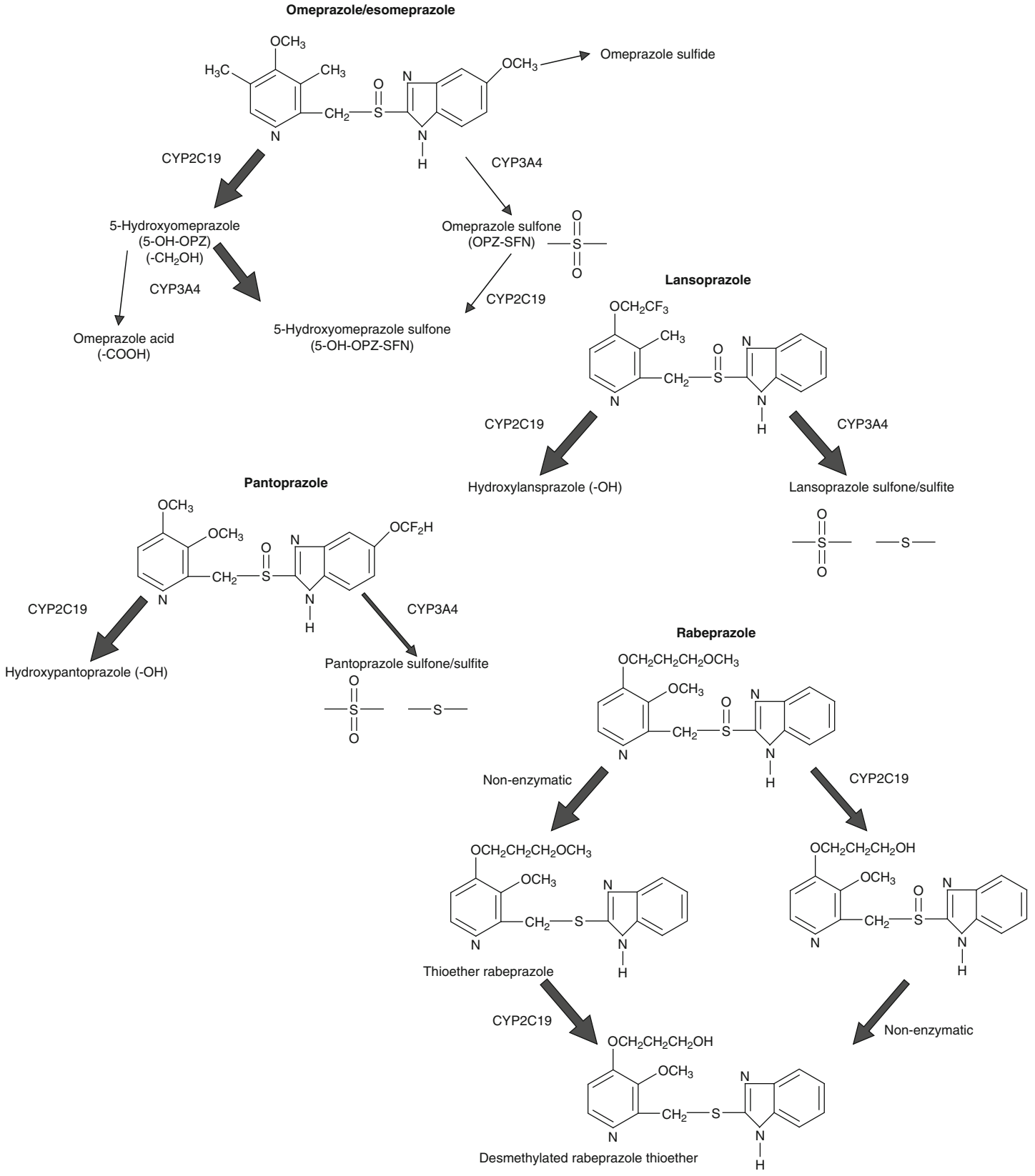

Fig. 1. Metabolic pathways of omeprazole, lansoprazole, pantoprazole, and rabeprazole in relation to CYP isoenzymes. The different weights of the arrows indicate the relative contribution of different enzyme pathways. CYP2C19 is involved in the metabolism of all proton pump inhibitors.

CYP2C19. There are genotypic differences that affect the activity of CYP2C19. Various genetic mutations involved in CYP2C19 polymorphism have been discovered in ethnically different populations.[11] However, interindividual differences in the activity of CYP2C19 can be explained by the combination of two point mutations, *CYP2C19**2 of exon 5 and *CYP2C19**3 of exon 4, in most cases.[12-14] The phenotypes resulting from polymorphism of this enzyme are generally classified into three genotype groups: rapid metabolizers (RMs: *1/*1), intermediate metabolizers (IMs: *1/*X), and poor metabolizers (PMs: *X/*X), where *1 represents the wild-type allele and *X represents the mutated allele. The nomenclature of genotype groups of *CYP2C19* varies in the literature; for example, *CYP2C19* genotype groups are classified into extensive metabolizers (EMs), IMs, and PMs in some papers.[15-17] However, in many important papers on CYP2C19,[18-38] the classification of EMs has included both *1/*1 homozygotes and *1/*X heterozygotes (= IMs), therefore, usage of the term 'EM' as the genotype of *1/*1 may be confusing. Accordingly, to avoid confusion for readers, the term 'RMs', rather than 'EMs', is used to denote homozygotes of *CYP2C19**1/*1 in this paper.

*CYP2C19**2 is a single base-pair mutation from guanine to adenine in exon 5 of *CYP2C19*, which creates a truncated nonfunctional protein. This defect accounts for approximately 75–83% of the PM allele in both Japanese and Caucasian subjects.[14] *CYP2C19**3 is a mutation from guanine to adenine at position 636 of exon 4 of *CYP2C19*, which creates a premature stop codon.[12] The frequencies of RMs, IMs, and PMs of this enzyme differ among different ethnic groups, with the incidence of PMs being higher in Asians than in Caucasians and Africans.[13,39-41] The *CYP2C19**3 allele is absent in Caucasians; in this ethnic group, the PM phenotype is mainly attributed to the *CYP2C19**2 allele alone. Representative frequencies of phenotypes and alleles in different ethnic groups are summarized in table I.

*CYP2C19**17 has been found to be associated with the ultra-rapid metabolizer (UM) phenotype of CYP2C19 (*17/*17 homozygotes).[45] There are ethnic difference in the frequency of this allele.[42,43,46] The allele frequency of *CYP2C19**17 is around 18% in Swedes and Ethiopians, but is only 4.4% in Chinese and 1.3% in Japanese populations (table I).[44,45]

2.2 Effect of CYP2C19 Polymorphism on the Pharmacokinetics of PPIs

When omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 20 mg are given, plasma concentrations of the three PPIs differ among the three different *CYP2C19* genotype groups (RMs, IMs, and PMs) [figure 2a].[47] Plasma omeprazole levels in the PM group are sustained for a long time after dosing. The mean value for the area under the plasma concentration-time curve of omeprazole in the PM group is about 13 times as high as that in the RM group (table II). Similar *CYP2C19* genotype-dependent differences in plasma PPI levels are observed with other PPIs such as lansopazole, rabeprazole, and esomeprazole (figure 2a and 2b, and table II).[22,47-50] Although there are some differences in individual PPIs, the plasma levels of all PPIs are generally influenced by *CYP2C19* genotypic differences.

There have been conflicting data on the influence of *CYP2C19**17 on the pharmacokinetics of PPIs.[51-55] The *CYP2C19**17 allele was first reported to be associated with ultra-rapid metabolism of a PPI in a Swedish group.[45,51]

Table I. Frequencies of CYP2C19 phenotypes and alleles in different populations

Ethnicity	Phenotype frequency				Allele frequency				Reference
	UM	RM	IM	PM	*1	*2	*3	*17	
White	0.042	0.69	0.19	0.028	0.66	0.12	NE	0.18	42
Caucasian	NE	0.69	0.28	0.028	0.83	0.17	0.00	NE	41
	0.042	0.620	0.301	0.036	0.593	0.181	0.006	0.220	43
Ashkenazi Jewish	0.026	0.68	0.22	0.018	0.70	0.12	NE	0.13	42
Japanese	0.015	0.366	0.453	0.188	0.579	0.279	0.128	0.013	44
	NE	0.349	0.463	0.188	0.58	0.29	0.13	NE	40
Chinese	NE	0.34	0.41	0.26	0.54	0.40	0.06	NE	13
African	NE	0.68	0.281	0.037	0.823	0.173	0.004	NE	39
African American	0.033	0.69	0.15	0.067	0.63	0.12	NE	0.19	42
Hispanic	0.023	0.74	0.2	0.0087	0.75	0.10	NE	0.10	42

IM = intermediate metabolizer; **NE** = not examined; **PM** = poor metabolizer; **RM** = rapid metabolizer; **UM** = ultra-rapid metabolizer.

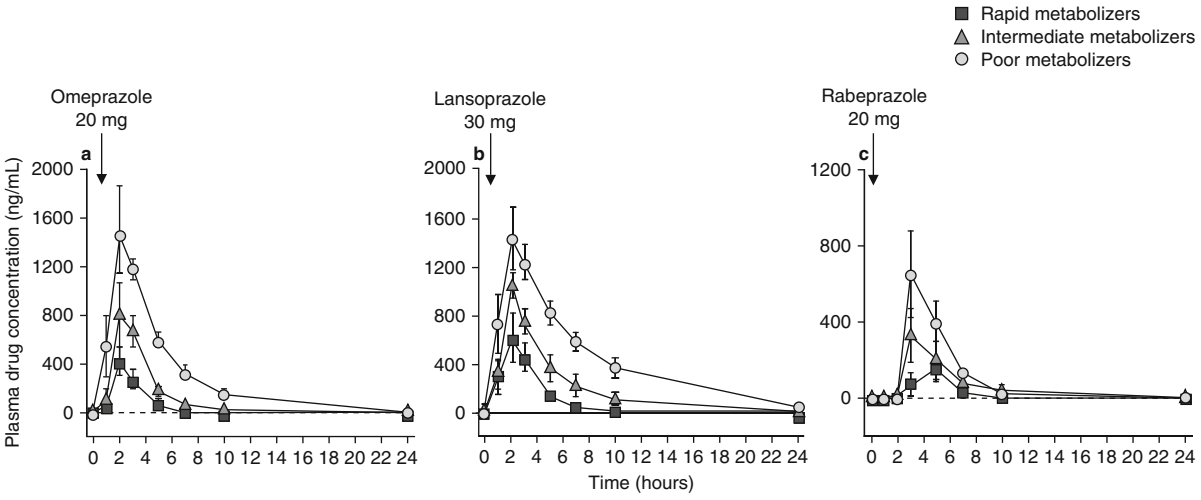

Fig. 2. Influence of CYP2C19 polymorphism on the pharmacokinetics of omeprazole, lansoprazole, and rabeprazole. Plasma concentrations of the three proton pump inhibitors were highest in the poor metabolizer group, intermediate in the intermediate metabolizer group, and lowest in the rapid metabolizer group. (Adapted from Shirai et al.[48] and Furuta et al.,[49] with permission.)

However, more recent reports from different institutions have indicated that *CYP2C19**17-associated differences in pharmacokinetics of PPIs are not significant.[52,53] A meta-analysis[56] of the impact of *CYP2C19**17 on the clinical outcomes of PPIs has indicated that the clinical impact of *CYP2C19**17/*17 is almost the same as that of *CYP2C19**1/*1, although *CYP2C19**17 is associated with an increased risk of bleeding in patients treated with clopidogrel.[42,57] Therefore, in contrast to data relating to clopidogrel, recent data have indicated that assignment of *CYP2C19**17 homozygotes as UMs, rather than RMs or EMs, is inadequate in the clinical setting of PPIs. Further accumulation of data is needed on the influence of the *CYP2C19**17 allele on clinical outcomes of acid-related disorders treated with PPIs.

2.3 Effect of CYP2C19 Polymorphism on Gastric Acid Inhibition with PPIs

Because plasma levels of PPIs differ among different *CYP2C19* genotype groups, the intragastric pH profiles also differ when a PPI (e.g. omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 20 mg) is administered (figure 3). The mean 24-hour intragastric pH is lowest in the RM group, intermediate in the IM group, and highest in the PM group.[47] The acid inhibition achieved by omeprazole, lansoprazole, or rabeprazole in the RM group is likely to become insufficient under the so-called standardized dosing scheme (table III).[47,59]

Several studies have analyzed whether the *CYP2C19* genotype influences the acid inhibition achieved by PPIs. For omeprazole,

Table II. Mean values of the area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}) of different proton pump inhibitors (PPIs) as a function of *CYP2C19* genotypes

PPI regimen	Timing of AUC_{24} measurement	Mean AUC_{24} (ng • h/mL)			RM : IM : PM ratio	Reference
		RMs	IMs	PMs		
Omeprazole 20 mg	Day 1	421	1 403	5 109	1 : 3.3 : 12.2	47
		524	1 096	5 607	1 : 2.1 : 10.7	48
	Day 8	1 057	2 418	7 153	1 : 2.3 : 6.8	48
Rabeprazole 20 mg	Day 1	696	1 609	2 329	1 : 2.3 : 3.3	48
	Day 8	464	1 398	2 437	1 : 3.0 : 5.3	48
Lansoprazole 30 mg	Day 8	1 980	4 775	10 663	1 : 2.4 : 5.4	49
Esomeprazole 20 mg	Day 5	3 280	7 280	9 190	1 : 2.2 : 2.8	50
Esomeprazole 40 mg	Day 7	16 208	21 038	24 059	1 : 1.3 : 1.5	22

IM = intermediate metabolizer; **PM** = poor metabolizer; **RM** = rapid metabolizer.

reports have shown that the acid inhibition achieved by once-daily dosing of 10 mg, 20 mg, or 40 mg was influenced by the *CYP2C19* genotype.[38,47,48,60-66] The acid inhibition achieved by once-daily dosing of esomeprazole 20 mg or 40 mg was also influenced by the *CYP2C19* genotype,[22,61,67,68] although dosing of 10 mg 4 times daily or 20 mg twice daily was not.[22] The acid inhibitory effect of lansoprazole 15 mg or 30 mg once daily was shown to depend on the *CYP2C19* genotype,[49,58,60,69,70] as was once-daily rabeprazole (10 mg and 20 mg) in most[26,60,65,67,68,71-76] but not all reports.[29,48,70] Interestingly, rabeprazole 10 mg twice daily was shown not to be influenced by the *CYP2C19* genotype status.[73] Thus, although the acid inhibition achieved by PPIs administered once daily appears to be influenced by the *CYP2C19* genotype, divided or frequent dosing seems to minimize the influence of *CYP2C19* genotypic differences.

2.4 Other Polymorphisms Associated with the Pharmacokinetics and Pharmacodynamics of PPIs

Because PPIs are absorbed from the small intestine, genetic polymorphism of the transporter of PPIs affects the pharmacokinetics and pharmacodynamics of these drugs. P-glycoprotein, an enzyme coded by the ATP-binding cassette, sub-family B (MDR/TAP), member 1 gene (*ABCB1*; previously known as multidrug resistance transporter gene 1 [*MDR1*]) is associated with absorption of PPIs from the small intestine, and is polymorphic. Kodaira et al.[77] studied the influence of the *ABCB1*

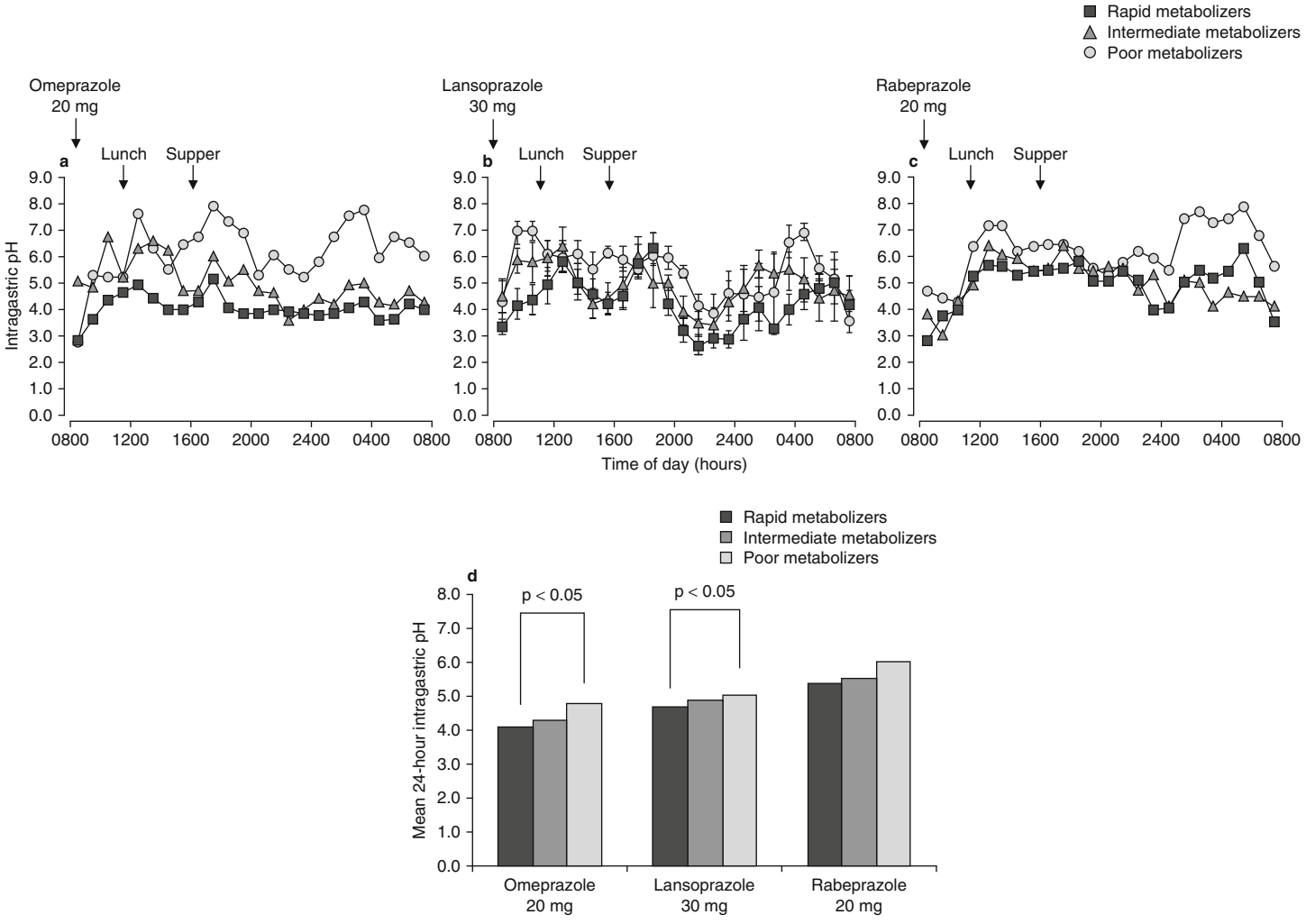

Fig. 3. (**a**–**c**) Profiles of intragastric pH values as a function of *CYP2C19* genotype status on day 7 for once-daily dosing of (**a**) omeprazole 20 mg, (**b**) lansoprazole 30 mg, and (**c**) rabeprazole 20 mg. Because intragastric pH is influenced by food, the timings of meals are indicated on the graphs. (**d**) Influence of CYP2C19 polymorphism on the mean 24-hour intragastric pH achieved by the different proton pump inhibitors. There were CYP2C19-phenotype-dependent differences in the mean 24-hour intragastric pH achieved by omeprazole and lansoprazole, but not rabeprazole. (Adapted from Shirai et al.[48] and Furuta et al.,[49] with permission.)

Table III. Median intragastric pH values achieved by different proton pump inhibitors (PPIs) as a function of *CYP2C19* genotypes

PPI regimen	Timing of pH measurement	Median intragastric pH			Reference
		RMs	IMs	PMs	
Omeprazole 20 mg	Day 1	2.1	3.3	4.5	47
		2.3	3.3	4.1	48
	Day 8	4.1	4.7	5.9	48
Lansoprazole 30 mg	Day 8	4.4	4.9	5.4	58
Rabeprazole 20 mg	Day 1	3.3	4.2	5.3	48
	Day 8	4.8	5.0	6.0	48
Esomeprazole 40 mg	Day 7	3.6	3.1	4.9	22

IM = intermediate metabolizer; **PM** = poor metabolizer; **RM** = rapid metabolizer.

3435C/T polymorphism on the pharmacokinetics and pharmacodynamics of lansoprazole in Japanese subjects and found that the plasma levels of lansoprazole were higher in subjects with the *ABCB1* 3435 TT genotype than in those with the CT or CC genotypes. However, there was no significant difference in the acid inhibition achieved by lansoprazole among different *ABCB1* 3435C/T genotype groups. They concluded that the influence of *ABCB1* polymorphism on the pharmacokinetics and pharmacodynamics of a PPI was smaller than that of *CYP2C19* polymorphism and could be disregarded in the clinical setting.

CYP3A4 is also associated with the metabolism of PPIs.[78] However, genotypes associated with CYP3A4 activity have not been fully elucidated.

3. Effect of CYP2C19 Polymorphism on Gastroesophageal Reflux Disease (GERD) Treatment by PPIs

Because GERD healing rates depend on the levels of acid inhibition,[79] and because acid inhibition achieved by a PPI dosed once daily differs among different *CYP2C19* genotypes, as noted above, the rates of healing of GERD by a PPI dosed once daily should theoretically be influenced by the *CYP2C19* genotype status.

The influence of *CYP2C19* genotypes on the rates of healing of GERD (erosive reflux esophagitis [RE] and non-erosive reflux disease [NERD]) has been evaluated in several studies. The clinical effect of some PPIs on RE were reported to depend on *CYP2C19* genotypes when a PPI was dosed once daily (table IV).[80-82,85-87] For example, when lansoprazole 30 mg was administered for 8 weeks to GERD patients with mucosal breaks (grades A–D in the Los Angeles Classification),[88] the rate of healing of mucosal breaks was lowest in the RM group and highest in the PM group, with intermediate healing rates observed in the IM group. The rate of healing of mucosal breaks in patients with grade C or D GERD who carried a *CYP2C19* RM genotype was dramatically low (1 of 6 patients [16.7%]; 95% CI 0.4, 64.1).[82] Similarly, Kawamura et al.[81] reported that the rate of healing of mucosal breaks in RM patients was the lowest among the three different *CYP2C19* genotype groups when they were treated with lansoprazole 30 mg once daily. This study indicated that acid inhibition achieved by a daily dose of lansoprazole 30 mg in the PM genotype group is clinically sufficient for GERD treatment, but that in IMs and RMs this dose might be insufficient in some cases.

On the other hand, the influence of *CYP2C19* polymorphisms on the rates of healing of GERD by rabeprazole and esomeprazole seems to differ from that observed with lansoprazole or omeprazole. Schwab et al.[83] reported that esomeprazole-induced healing of GERD was unrelated to the *CYP2C19* genotype. Ariizumi et al.[84] reported that the therapeutic effects of rabeprazole 10 mg/day on RE were sufficient and were not influenced by *CYP2C19* polymorphism (table IV). The involvement of CYP2C19 in the metabolism of rabeprazole and esomeprazole is relatively minor in comparison with its influence on the metabolism of omeprazole and lansoprazole, which might contribute to the lack of influence of *CYP2C19* polymorphism on the GERD cure rates observed with rabeprazole

Table IV. Influence of CYP2C19 polymorphism on the rates of cure of erosive esophagitis achieved by different proton pump inhibitors (PPIs)

PPI regimen	Duration of therapy	Rates of cure of erosive esophagitis (%)			p-Value	Reference
		RMs	IMs	PMs		
Omeprazole 20 mg	4 weeks	43 (n = 25)	95 (n = 33)		0.04	80
Lansoprazole 30 mg	8 weeks	77.4 (n = 31)	95.0 (n = 40)	100.0 (n = 17)	<0.05	81
		45.8 (n = 24)	67.9 (n = 28)	84.6 (n = 13)	<0.05	82
Esomeprazole 40 mg	4 weeks	50.7 (n = 148)	43.1 (n = 51)	50.0 (n = 6)	NS	83
Rabeprazole 10 mg	8 weeks	86.1 (n = 36)	92.0 (n = 50)	82.4 (n = 17)	NS	84

IM = intermediate metabolizer; **PM** = poor metabolizer; **RM** = rapid metabolizer; **NS** = not significant.

or esomeprazole. Because the acid inhibitory potency of rabeprazole is higher than those of omeprazole and lansoprazole,[89] the plasma levels of rabeprazole achieved by RMs might be sufficient to inhibit acid secretion to the levels needed for GERD treatment.

Recurrence of RE during maintenance therapy with a PPI depends on *CYP2C19* genotypes. The symptomatic recurrence rate in RE patients treated with lansoprazole 15 mg was lowest in RMs, and that in PMs was the highest of the three groups.[86] Kawamura et al.[85] reported that *CYP2C19* genotypes influenced the remission of RE during maintenance therapy with lansoprazole. Saitoh et al.[87] reported that *CYP2C19* genotypes affected the rate of recurrence of GERD symptoms during PPI maintenance therapy. Together, these studies suggest that initial and maintenance PPI therapy for RE is influenced by *CYP2C19* genotypes.

However, the effect of *CYP2C19* genotypes does not seem potent in patients with NERD. Kinoshita et al.[90] and Uemura et al.[91] independently studied the influence of *CYP2C19* genotypes on the treatment of NERD by a PPI and concluded that the *CYP2C19* genotype was not associated with therapeutic outcomes. However, Furuta et al.[92] reported that a step-up of the PPI dose (e.g. from rabeprazole 10 mg once daily to rabeprazole 10 mg twice daily and to 20 mg twice daily) was effective for patients who were refractory to the PPI at the standard dose, suggesting that insufficient acid inhibition is one of the reasons for therapeutic failure of a PPI in patients with NERD. Further studies are needed to verify the influences of *CYP2C19* genotypes on the efficacy of a PPI for NERD.

In summary, *CYP2C19* genotype status is considered to be one of the predictable determinants of the results of PPI-based therapy for RE. Therefore, an individualized therapeutic strategy based on the individual *CYP2C19* genotype status is expected to increase the healing rates achieved by initial therapy with a PPI for GERD.

4. Strategies for Sufficient Acid Inhibition in Rapid Metabolizers of CYP2C19

As discussed above, one of the reasons for failure of PPI therapy for GERD is insufficient acid inhibition achieved by the PPI in patients with RM genotypes of *CYP2C19*. Overcoming the insufficient acid inhibition achieved by a PPI in RMs should result in an increase in GERD cure rates. For this purpose, several approaches have been tested. The acid inhibitory effect of histamine H_2 receptor antagonists (H2RAs), such as famotidine, is not affected by the *CYP2C19* genotype status and was shown to be superior to that of lansoprazole for controlling nocturnal intragastric pH in RM patients.[58] Sugimoto et al.[75] also administered an H2RA to RMs and reported that the addition of famotidine could achieve sufficient acid inhibition in such patients. Furuta et al.[93] reported that concomitant use of famotidine and lansoprazole yielded sufficient acid inhibition in *CYP2C19* RMs. Adding an evening dose of an H2RA to a morning dose of a PPI appears to be effective for control of nocturnal acid breakthrough in individuals who are resistant to standard PPI treatment.[94-96] Therefore, addition of an H2RA is a useful strategy to overcome the insufficient acid inhibition achieved by a PPI in RMs.

Another approach to this problem is to increase the dosing schedule for a PPI. As noted above, frequent divided dosing of a PPI can minimize the influence of *CYP2C19* genotypes. When lansoprazole 30 mg is administered four times daily in order to sustain plasma lansoprazole levels all day long (figure 4a), complete acid inhibition can be achieved even in RMs (figure 4b).[49] Interestingly, the peak plasma concentration (C_{max}) of lansoprazole in RMs receiving this dosage was not increased in comparison with that achieved by once-daily dosing of 30 mg (figure 4a) and was not as high as that observed in PMs, although sufficient acid inhibition was achieved in RMs. Sugimoto et al.[76] reported that four-times-daily dosing of rabeprazole 10 mg achieved higher acid inhibition than that achieved by once-daily dosing of rabeprazole 40 mg. Similarly, Lou[22] reported that acid inhibition achieved by esomeprazole 20 mg twice daily or 10 mg four times daily did not differ among *CYP2C19* genotype groups, although that achieved with esomeprazole 40 mg once daily did differ. Therefore, for *CYP2C19* RMs, the optimal dosing scheme for a PPI is twice daily to four times daily. This strategy should be used when a patient is refractory to a PPI dosed once daily.

5. Is Individualized Therapy for GERD Based on Genetic Testing Useful?

Unfortunately, there have been no studies of pharmacogenomics-guided therapies for GERD. As discussed above, the efficacy of PPIs depends on *CYP2C19* genotypes; therefore, *CYP2C19* genotype-guided adjustment of the dosing of a PPI is preferable. If the *CYP2C19* genotype can be determined before the study, an optimal dosing scheme for a PPI can be developed in each patient, which is expected to increase the rate of cure of GERD during initial therapy. The recommended initial dosing schedules are as follows: four-times-daily dosing of a PPI at the standard dose for RMs, twice-daily dosing of a PPI at the standard dose for IMs, and once-daily dosing of a PPI at the standard dose for PMs. Thereafter, the dose of the PPI can be

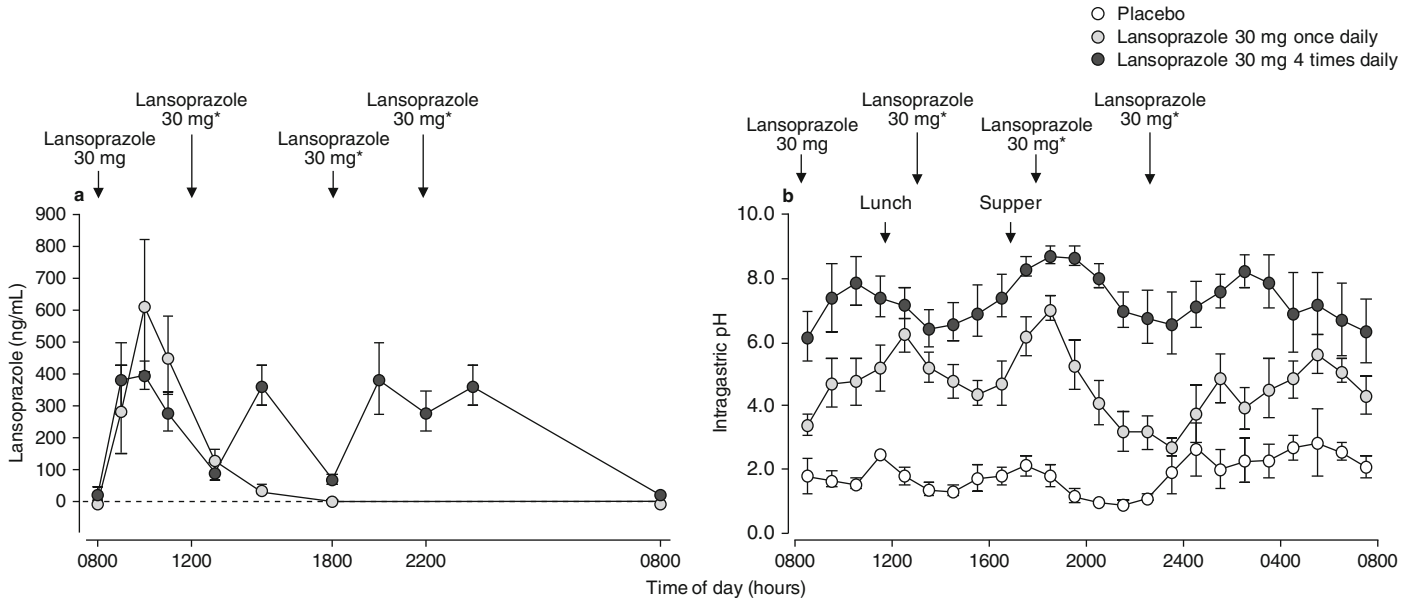

Fig. 4. (**a**) Mean (± standard error) plasma concentration-time curves and (**b**) mean (± standard error) intragastric pH values versus time for lansoprazole after the final dosing of lansoprazole 30 mg once daily and lansoprazole 30 mg 4 times daily for 8 days in 5 patients with CYP2C19 rapid metabolizer genotypes. With 4-times-daily dosing of lansoprazole 30 mg, plasma levels of lansoprazole are sustained during each of the dosing intervals, thus complete acid inhibition (i.e. an intragastric pH of approximately 7.0) can be achieved. * Indicates dosing of lansoprazole 30 mg 4 times daily. (Reproduced from Furuta et al.,[49] with permission.)

decreased (or increased) on the basis of the response of each patient to the PPI therapy (step-down or step-up) [figure 5]. This strategy is expected to increase the initial rates of response of GERD to PPI therapy.

6. Interaction of PPIs with Other Drugs

Patients taking a PPI sometimes take other medicines, some of which interact with the PPI. Therefore, the prescribing clinician must know about drug-drug interactions between PPIs and other drugs.

PPI-induced changes in gastric pH values sometimes influence the absorption of other drugs. Inhibition of gastric acid secretion increases the absorption of acid-labile drugs such as digoxin and sulfonyl urea, and weak acids such as diazepam, aspirin, and the diuretic furosemide. On the other hand, inhibition of acid secretion decreases the absorption of weak acids such as ketoconazole, itraconazole, dipyridamole, tetracycline, cephalosporin antibiotics, gefitinib, and erlotinib.[9,97,98] To avoid this interaction in the case of ketoconazole, it is recommended that the PPI is taken with cola, because the acidity of cola (~pH 2.5) lessens the inhibition of ketoconazole absorption by the PPI.[99]

PPIs sometimes interact with CYP substrates. Stedman and Barclay[100] summarized the drug-drug interaction of different PPIs via CYPs and reported that there was some variation in their potential for drug interactions due to differences in enzyme inhibition. Kodaira et al.[101] reported the effect of different PPIs on CYP activity assessed by the [^{13}C]-aminopyrine breath test in relation to CYP2C19 polymorphisms. They reported that different PPIs inhibited CYP activity to different extents. However, a higher PPI dose (e.g. omeprazole 80 mg)

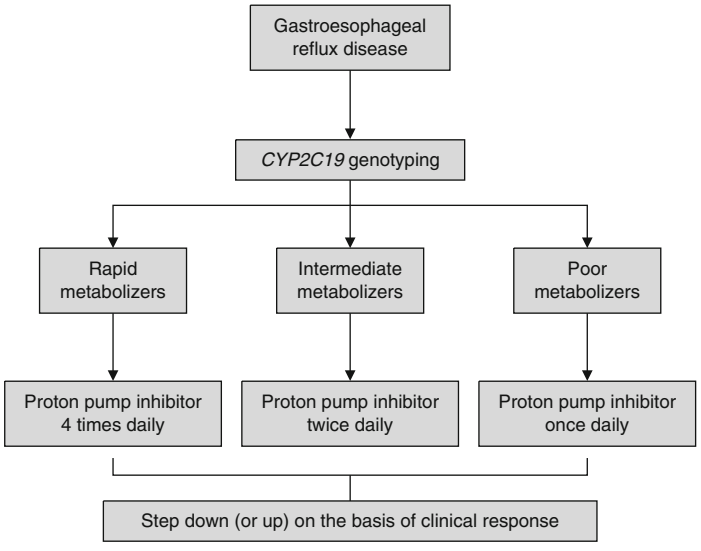

Fig. 5. An example of strategies for individualized proton pump inhibitor therapy for gastroesophageal reflux disease, based on a genotyping test for *CYP2C19*.

seemed to further inhibit CYP2C19 metabolic activity in RMs but increased it in PMs, indicating that a higher dose of a PPI induces other enzymes, such as CYP1A2.

The interaction between PPIs and clopidogrel has been focused on. In 2008, the consensus and guidelines of the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA) on antiplatelet therapy were published,[102-104] and they recommended that patients with a risk of peptic ulcer and/or those who were treated with two or more antiplatelet agents be treated with a PPI. However, clopidogrel is metabolically activated by CYP2C19 – the plasma level of the active metabolite of clopidogrel depends on the activity of CYP2C19. As a matter of fact, the inhibitory effect of clopidogrel on platelet aggregation depends on *CYP2C19* genotypes[105] and is also associated with clinical events.[106] Moreover, concomitant use of clopidogrel and a PPI induces a drug-drug interaction via CYP2C19, resulting in decreased activation of clopidogrel. Juurlink et al.[107] reported that concomitant therapy with a PPI was associated with an increased risk of reinfarction. Ho et al.[108] reported that concomitant use of clopidogrel and a PPI was associated with an increased risk of adverse outcomes compared with use of clopidogrel without a PPI, and they suggested that use of a PPI might be associated with attenuation of the benefits of clopidogrel. These reports suggest that there are benefits (i.e. gastric protection) and risks (i.e. attenuation of clopidogrel efficacy) with concomitant use of a PPI in patients undergoing antiplatelet therapy including clopidogrel. This is the therapeutic dilemma of prophylactic use of PPI in antiplatelet therapy.

Furuta et al.[109] studied the effects of omeprazole, lansoprazole, and rabeprazole on the antiplatelet functions of clopidogrel in relation to *CYP2C19* genotype status and found that the three PPIs attenuated the antiplatelet functions of clopidogrel to different degrees and that the levels of attenuation of clopidogrel by PPIs depended on *CYP2C19* genotype status. They found that separate dosing of clopidogrel and omeprazole could not avoid this interaction (figure 6a). Although the efficacy of clopidogrel was decreased by a PPI in *CYP2C19* RMs, the levels of antiplatelet function of clopidogrel after attenuation by a PPI in this group were generally not problematic (i.e. they were rarely decreased to the levels of a 'low responder' [inhibition of platelet aggregation <30%]) [figure 6b]. On the other hand, in patients with an IM genotype of *CYP2C19*, a conversion from responder to low-responder status occurs easily. Patients with *CYP2C19* PM genotypes were low responders irrespective of PPI use. Therefore, the influence of a PPI on the activity of clopidogrel also depends on *CYP2C19* genotypes.

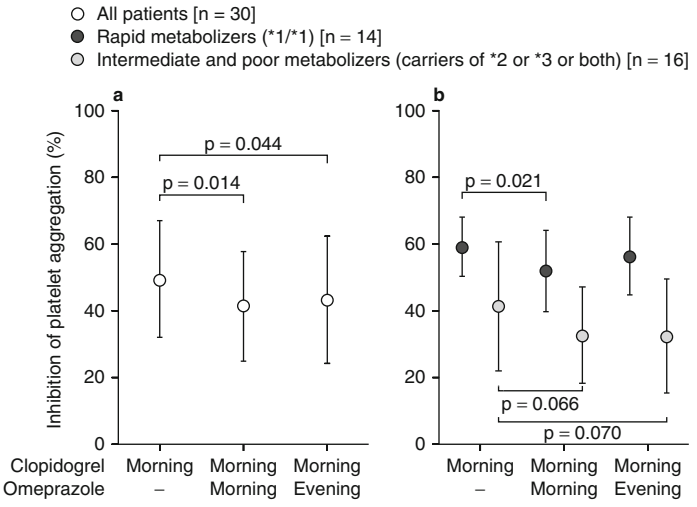

Fig. 6. Effects of morning or evening dosing of omeprazole on the efficacy of clopidogrel (**a**) in all patients and (**b**) in different *CYP2C19* genotype groups. The decreased efficacy of clopidogrel caused by concomitant dosing of omeprazole was not restored by separate dosing of omeprazole overall (**a**), but when the patients were analyzed separately according to *CYP2C19* genotype (**b**), it was restored in CYP2C19 rapid metabolizers by separate dosing of omeprazole. In carriers of *CYP2C19**2 or *3 or both (intermediate and poor metabolizers), omeprazole appeared to decrease the efficacy of clopidogrel, which did not seem to be restored by separate dosing of omeprazole. (Reproduced from Furuta et al.,[109] with permission.)

Although prospective studies have indicated that the influence of PPIs on the clinical effect of clopidogrel is not problematic,[110,111] all pharmacokinetic studies have indicated the presence of a drug-drug interaction between PPIs and clopidogrel. Patients receiving dual antiplatelet therapy who are at risk of gastrointestinal bleeding should be treated with a PPI. However, clinicians must take this interaction into consideration for careful follow-up of patients.

7. Conclusion

The clinical effects of PPIs depend on the *CYP2C19* genotypes of patients, as discussed in this review. Therefore, adjustments of the dose and dosing schedule for a PPI according to the *CYP2C19* genotype should be useful for optimal PPI treatment in patients with GERD. The pharmacogenomics-based strategy requires genotyping tests in advance and therefore seems more costly, but we expect that such a cost could be offset by several benefits obtained from the higher cure rates achieved by the initial pharmacogenomics-based treatment.

Acknowledgments

The Center for Clinical Research at Hamamatsu University School of Medicine has received grants from Takeda Pharmaceutical Co., Ltd.,

AstraZeneca KK, and Eisai Co., Ltd., and Drs. Furuta and Sugimoto have received lecture fees from those companies. The authors have no other conflicts of interest that are directly relevant to the content of this article.

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