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REVIEW

Efficacy of esomeprazole in treating acid-related diseases in Japanese populations

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Abstract: Esomeprazole (Nexium®; AstraZeneca), the S-isomer of omeprazole, is the first proton pump inhibitor (PPI) to be developed as an optical isomer. Compared with omeprazole, esomeprazole has an improved pharmacokinetic profile with regards to CYP2C19 (S-mephenytoin 4′-hydroxylase) genotype, showing increased systemic exposure and less interindividual variability. Further, esomeprazole is a more potent acid inhibitor than other currently available PPIs and is therefore used as a first-line drug for acid-related diseases. While esomeprazole has been available in a number of countries worldwide, the compound only received authorized permission to be marketed in Japan in September 2011. The standard esomeprazole dose in Japan for the treatment of peptic ulcers and gastroesophageal reflux disease (GERD) is 20 mg. Other advised dosages are 10 mg for nonerosive reflux disease and 20 mg twice-daily dosing for eradication of *Helicobacter pylori*. In Japanese, the effective rate of esomeprazole 20 mg during 24 weeks for GERD patients is 92.0% (88.0%–96.0%), while the prevention of peptic ulcer development using 20 mg for 24 weeks in patients treated with nonsteroidal anti-inflammatory drugs is 96.0% (92.8%–99.1%). Although clinical data are limited, the usefulness of esomeprazole is expected in Japanese subjects given the reduced prevalence of CYP2C19 rapid metabolizers in Japan compared with Western countries.

Keywords: esomeprazole, PPI, CYP2C19, peptic ulcer, GERD, *H. pylori*

Introduction

A wide number of proton pump inhibitors (PPIs) have been developed for the treatment of acid-related diseases. PPIs are currently the first-line treatment against acid-related diseases such as gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) and Zollinger–Ellison syndrome, and are used in combination with antibiotics for the eradication of *Helicobacter pylori*.[1–4] PPIs function by first being absorbed into the small intestine and reaching the gastric parietal cells via systemic circulation, where they then disturb proton pump (H^+/K^+-ATPase) activity by irreversibly binding to the pumps, thereby resulting in potent acid inhibition.[5,6] In Japan, four kinds of PPIs are available: omeprazole, lansoprazole, rabeprazole, and esomeprazole, the last of which has been approved for use in Japan only since September 2011. In this review, we focus on esomeprazole, newly available in Japan, and its efficacy in treating acid-related diseases in Japanese patients.

Characteristics of esomeprazole

PPIs are substituted benzimidazoles that exist as a racemic mixture of R- and S-isomers. Esomeprazole (Nexium®; AstraZeneca, Wilmington, DE) is the S-isomer of the PPI

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omeprazole and is the first single-isomer PPI to be developed for the treatment of acid-related diseases. In general, esomeprazole more effectively inhibits gastric acid secretion than omeprazole, particularly during daytime.[7–9] Esomeprazole differs from both its parent compound as well as other PPIs in that it has a lower first-pass hepatic metabolism and slower plasma clearance, which results in higher plasma concentrations.[7–9] This increased systemic bioavailability offers potentially better clinical efficacy and more effective management of acid-related diseases.

In Japan, the standard dose of esomeprazole for treatment is 20 mg once-daily dosing (od), which is half the 40 mg od dose more commonly used in several Western countries. Overall, the Japanese national health insurance system permits esomeprazole use for the treatment of gastric ulcers for 8 weeks (20 mg od), duodenal ulcers for 6 weeks (20 mg od), erosive GERD for 8 weeks (10–20 mg od), NERD for 8 weeks (10 mg od), for the treatment of Zollinger–Ellison syndrome (20 mg od), for the prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers (20 mg od), and for the eradication of *H. pylori* (20 mg twice-daily [bid]) for 7 days. However, because it has only recently been available in Japan, information on the pharmacological and clinical effects of esomeprazole in Japanese populations is limited.

Pharmacokinetics of esomeprazole

In human liver microsomal experiments, the metabolic rate significantly differed among three types of S-omeprazole (esomeprazole), R-omeprazole, and a racemic mixture of the two (omeprazole), with the metabolic rate for esomeprazole in relation to drug metabolic enzyme being substantially lower than that for R-omeprazole or omeprazole.[8] The sum of the intrinsic clearance of all three metabolites (sulfone, hydroxyl, and 5-*O*-desmethyl metabolites) was 14.6 and 42.5 mL/min/mg protein for esomeprazole and R-omeprazole, respectively (Figure 1).[7] The maximum plasma esomeprazole concentrations (C_{max}) attained with esomeprazole were higher than those observed for the other two drugs (Table 1).[8] For reference, single 20 mg oral doses of esomeprazole generally give a C_{max} value of 0.5–1.8 mg/L within 1–3 hours of administration in Western populations.[8–10] Respective area-under-the-curve (AUC) values of esomeprazole, R-omeprazole, and omeprazole were 1.52, 0.62, and 1.04 μmol · hour/L on Day 1 and 2.84, 0.68, and 1.63 μmol · hour/L on Day 5. Additionally, the AUCs of esomeprazole at 20 and 40 mg were over 1.8 and 5.0 times higher than values for omeprazole 20 mg,[9] suggesting that after repeated administration, the C_{max} values of esomeprazole and omeprazole increase by approximately 50%–80% and 40%–50%, respectively, compared with that on Day 1,[8,10] and that the AUC levels of esomeprazole and omeprazole increase by approximately 80% and 50%, respectively, while that of R-omeprazole is almost unchanged (Table 1).[8] This change in drug exposure after repeated administration of esomeprazole and omeprazole may be due to an inhibition of cytochrome P450 (CYP) 2C19, one of the main drug metabolic enzymes for esomeprazole and omeprazole.

In another Phase I study of esomeprazole conducted by AstraZeneca in a Japanese population, the AUC and C_{max} values on Day 5 were approximately 80%–100% higher than on Day 1, findings consistent with those in Western populations (Table 1).[11] However, respective AUC values on Days 1 and 5 were 3.23 and 5.99 μmol · hour/L, respectively, values higher than those in Western populations (Table 1). This discrepancy may be due to differing frequencies of different S-mephenytoin 4′-hydroxylase (CYP2C19) genotype status

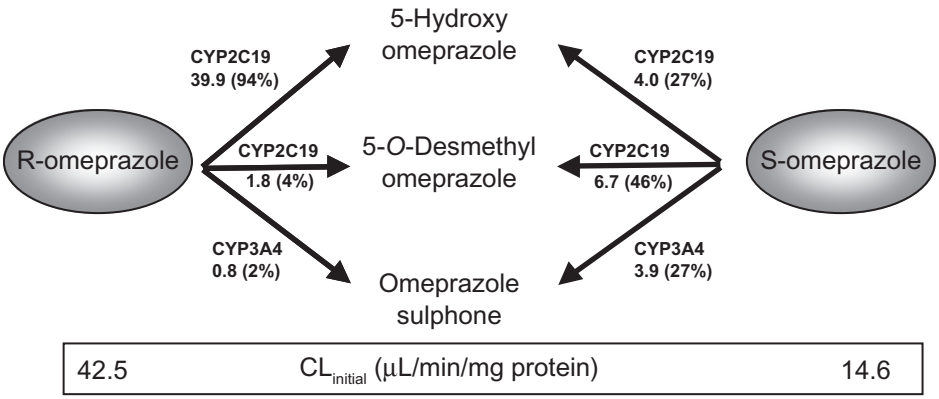

Figure 1 Clearance of R-omeprazole and S-omeprazole in relation to CYP2C19 and CYP3A4.[7] Clearance was 14.6 and 42.5 μL/min/mg protein for esomeprazole and R-omeprazole.

Table 1 Pharmacokinetic values for esomeprazole 20 mg

	Dosage regimens	Day	S-omeprazole	Racemic	R-omeprazole
Hassan-Alin et al[8] (Sweden)	AUC (ng · hour/mL)	1	1.5 (0.9–2.5)	1.0 (0.6–1.7)	0.6 (0.4–1.0)
		5	2.8 (1.7–4.8)	1.6 (1.0–2.8)	0.7 (0.4–1.2)
	C_{max} (μmol/L)	1	1.3 (0.9–1.8)	1.0 (0.8–1.4)	0.7 (0.5–1.0)
		5	1.8 (1.3–2.6)	1.4 (1.0–2.0)	0.7 (0.5–1.0)
	$t_{1/2}$ (hour)	1	0.8 (0.6–0.9)	0.7 (0.5–0.8)	0.5 (0.4–0.6)
		5	1.0 (0.8–1.2)	0.8 (0.6–1.0)	0.5 (0.4–0.7)
Andersson et al[10] (Sweden)	AUC (ng · hour/mL)	1	1.4 (1.0–2.3)		
		5	3.1 (2.1–4.6)		
	C_{max} (μmol/L)	1	1.7 (1.3–2.2)		
		5	2.6 (2.0–3.2)		
	$t_{1/2}$ (h)	1	0.7 (0.6–1.0)		
		5	1.1 (0.9–1.4)		
AstraZeneca[11] (Japan)	AUC (ng · hour/mL)	1	3.2 (2.3–4.5)		
		5	6.0 (4.3–8.4)		
	C_{max} (μmol/L)	1	1.4 (1.1–1.9)		
		5	2.6 (1.9–3.4)		
	$t_{1/2}$ (h)	1	1.1 (0.9–1.3)		
		5	1.3 (1.1–1.5)		

Notes: Maximum plasma concentration (C_{max}; ng/mL), plasma half-life time ($t_{1/2}$; hour), and area under the plasma concentration-time curve (AUC; ng · hour/mL) are given as median values (range).

among geographic populations[12–14] and to the prevalence of poor metabolizers (PMs) in that Phase I study.

Pharmacodynamics as acid-inhibiting drugs

While acid inhibition attained with esomeprazole, R-omeprazole, and omeprazole pharmacodynamics closely correlates to their respective AUC values, an observation true for other PPIs as well,[15,16] esomeprazole tends to show higher AUC values and more pronounced acid suppression than its related compounds.[9] In Western populations, esomeprazole at 40 mg maintains a percent of time of intragastric pH >4 for approximately 6 hours longer than omeprazole at 20 mg (16.8 vs 10.5 hours) and 4 hours longer than esomeprazole at 20 mg (16.8 vs 12.7 hours).[9] In general, esomeprazole is more effective at inhibiting potent acid secretion at 40 mg than at 20 mg, which is why many Western countries have established 40 mg as the standard dose for the treatment of acid-related diseases. However, in Japanese, the respective percent of time of intragastric pH >4 with esomeprazole at 40 and 20 mg and omeprazole at 20 mg are 62.39% ± 14.40% (n = 40), 68.49% ± 8.09% (n = 37), and 58.91% ± 14.40% (n = 38),[11] respectively, suggesting little difference in acid inhibition at esomeprazole 40 or 20 mg in Japanese. Therefore, because acid inhibition attained with esomeprazole in Japanese may be more potent than Western populations, esomeprazole 20 mg was selected as the standard dose.

In a randomized crossover study using 108 *H. pylori*-negative subjects, the percent of time of intragastric pH >4 on Day 5 was significantly increased following esomeprazole 20 mg compared with lansoprazole 15 mg (50.4% vs 43.0%; $P = 0.03$) and rabeprazole 10 mg (59.8% vs 51.7%; $P = 0.01$).[17] However, rabeprazole at 20 mg increased intragastric pH compared with esomeprazole at 20 mg on Day 1 and showed a higher AUC and intragastric pH on Day 1[18] while also producing greater acid suppression on Day 1 than esomeprazole at 40 mg, particularly at night.[19] Findings from these studies suggest that rabeprazole has a faster onset of acid inhibitory action than esomeprazole at either 20 or 40 mg from Day 1,[19] although esomeprazole remains the most effective PPI from Day 5.[20] Physicians should therefore consider the time and onset of treatment when selecting a PPI.

PPI-metabolizing enzyme CYP2C19 and its genotypes

PPIs undergo extensive hepatic metabolism by the CYP system (Figure 2).[21] Given that the principal enzyme related to the metabolism of PPIs is CYP2C19, it follows then that polymorphisms in CYP2C19 influence PPI pharmacokinetics and pharmacodynamics. Although more than 20 variant alleles of CYP2C19 have been identified, in Japanese the majority of individuals can be classified into the three genotypes, rapid extensive metabolizers (RMs), intermediate extensive metabolizers (IMs), and PMs, by identifying the CYP2C19 wild-type (CYP2C19 *1) gene and the two mutated alleles,

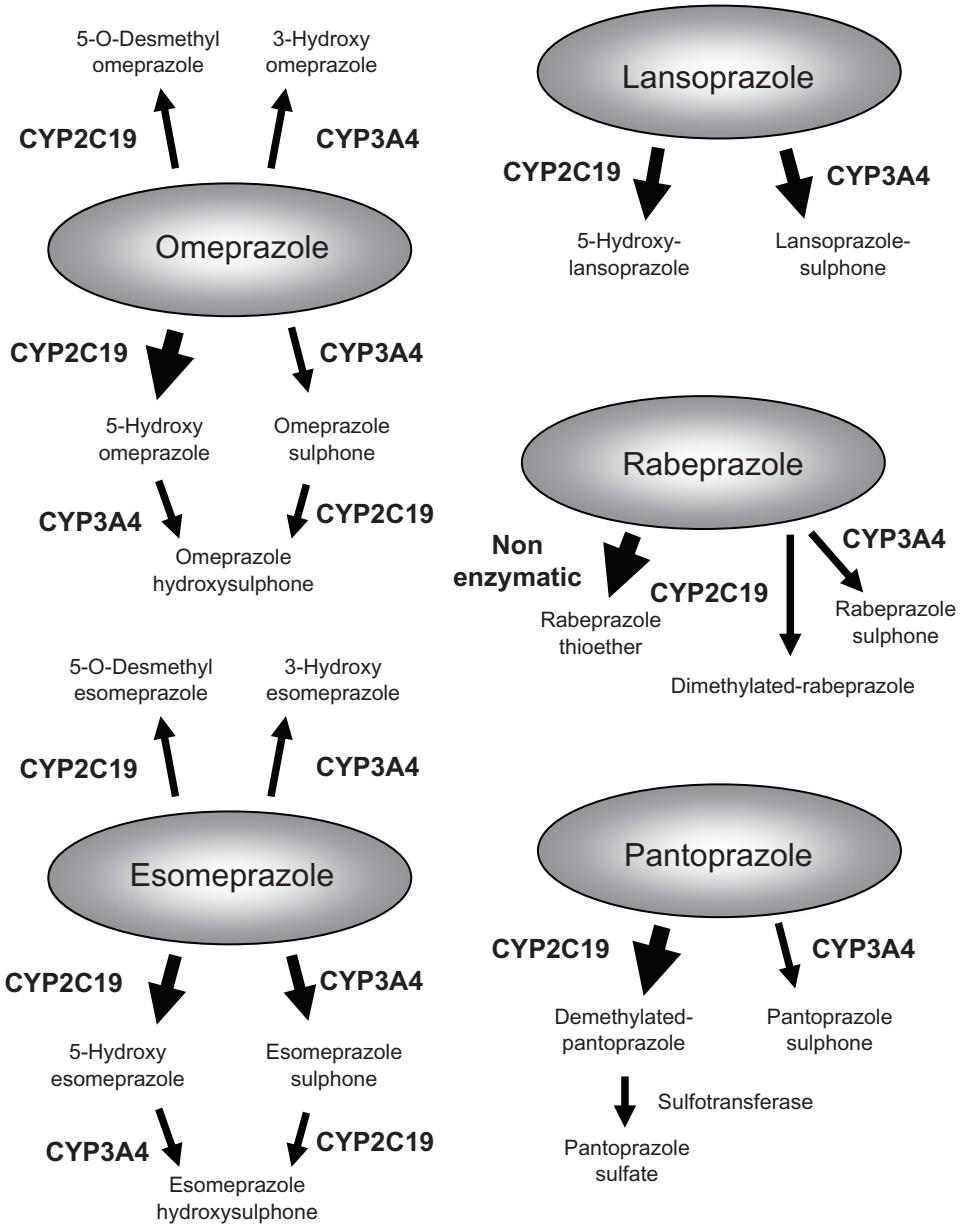

Figure 2 Metabolic pathways of esomeprazole, omeprazole, lansoprazole, rabeprazole, and pantoprazole in relation to cytochrome P450 isoenzymes, CYP2C19 and CYP3A4.
Note: Weight of arrows indicates the relative contribution of different enzyme pathways.

CYP2C19**2* (*2) in exon 5 and CYP2C19**3* (*3) in exon 4.[13,21–23] Although an ultrarapid metabolizer (CYP2C19**17*) has also been reported,[24] its allele carrier incidence in Japan is much lower (2%) than in Western populations.[25]

Interethnic differences in the frequency of PMs are quite variable, with frequency among Asians being 5–10 times that in other populations (2.5%–3.5% in Caucasians, 13.4%–19.8% in Chinese, 12.6% in Koreans, and 18.0%–22.5% in Japanese).[12–14] Additionally, the C_{max} and AUC values of a given PPI differ among the three major CYP2C19 genotype groups, with the highest values seen in PMs and lowest in RMs.[16,26,27] Further, the metabolic clearance value in PMs is significantly lower than in RMs or IMs,[16,26–28] while greater acid inhibition by PPIs can be observed in PMs due to differing pharmacokinetics in the genotype groups (Figure 3A–C).[26–30]

The in vitro formation of the 5-hydroxy and sulfone metabolites for both esomeprazole and R-omeprazole is mediated by CYP2C19 and CYP3A4.[7] The proportion of the hydroxy metabolite from esomeprazole is less than that from R-omeprazole, while the proportion of the sulfone from esomeprazole is more, indicating that esomprazole is less

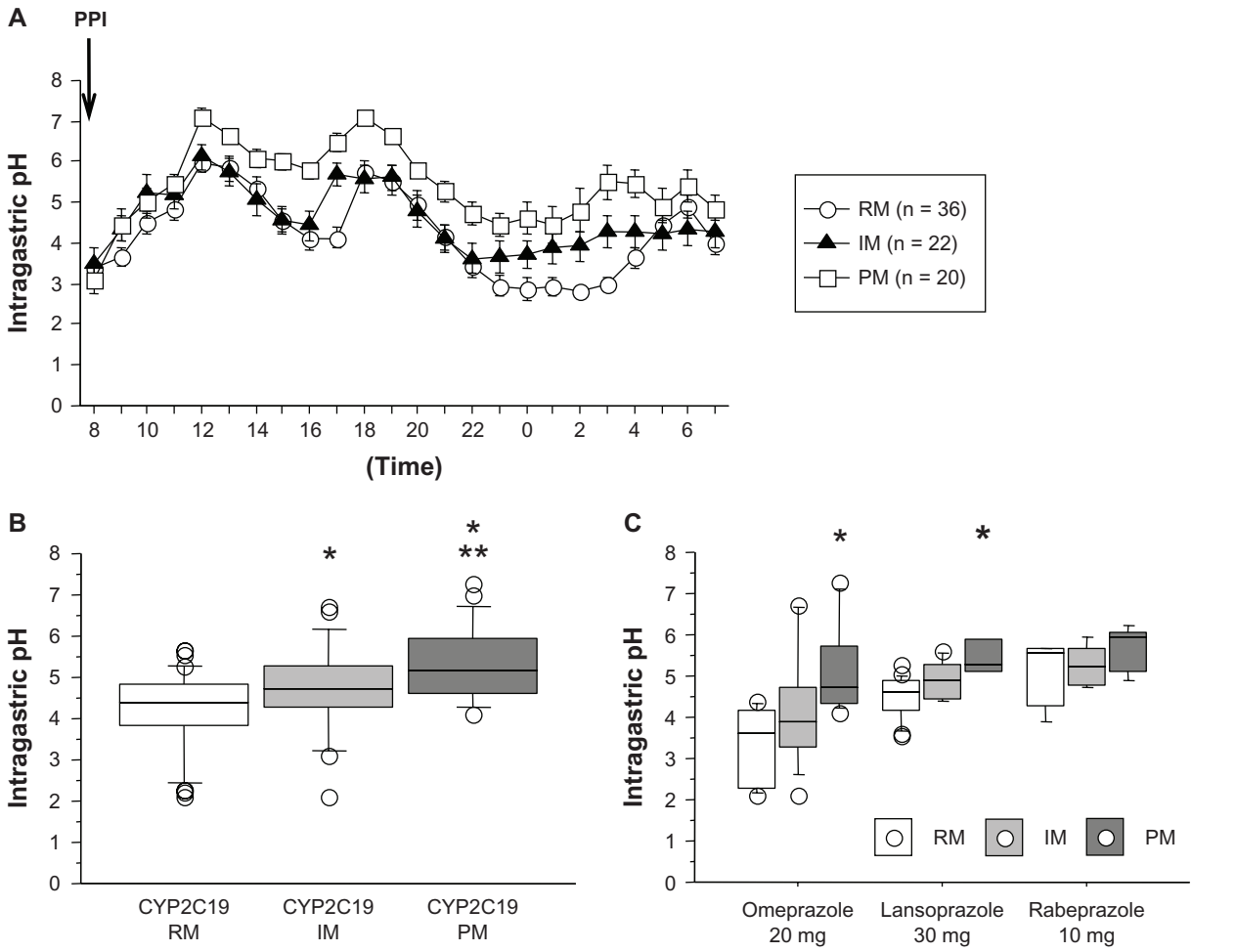

Figure 3 The 24-hour intragastric pH profiles after omeprazole 20 mg, lansoprazole 30 mg or rabeprazole 10 mg, od as a function of the CYP2C19 genotype group (**A**), and median 24-hour intragastric pH values in standard dose of PPI (**B**) and median 24-hour intragastric pH values in omeprazole, lansoprazole, or rabeprazole among different CYP2C19 genotype status (**C**).
Notes: *$P < 0.05$ (vs. CYP2C19 RM); **$P < 0.05$ (vs. CYP2C19 IM).
Abbreviations: RM, rapid extensive metabolizer; IM, intermediate extensive metabolizer; PM, poor metabolizer; PPI, proton pump inhibitor; od, once daily dose.

dependent on CYP2C19 than CYP3A4 for its metabolism than R-omeprazole. Because the clearance is 14.6 and 42.5 µL/min/mg protein for esomeprazole and R-omeprazole,[7] respectively, the effect of esomeprazole may be less than 50% that of omeprazole depending on the genotype (Figure 1). Similarly, the contribution of CYP2C19 to systemic exposure seems more pronounced when using lansoprazole (AUC ratio of PM/extensive metabolizer, 3.7–4.6) than esomeprazole (3.1).[31]

A Phase I study of esomeprazole in Japan showed that the AUC and C_{max} in CYP2C19 PMs is higher than that in RMs or IMs (Table 2).[11] Because the gastric acid suppression attained by PPI is correlated to total drug exposure, these differences should be considered when treating with esomeprazole.

Treatment for peptic ulcers

The neutralization of intragastric pH levels using appropriate medications is important in treating peptic ulcers and prevention of rebleeding from peptic ulcers.[32] Low-dose aspirin (LDA) is associated with adverse gastrointestinal effects, particularly in patients with increased gastrointestinal risk, which includes the elderly, those with a history of peptic ulcers, and those receiving concomitant treatment with other anti-platelet or anti-coagulant drugs.[33,34] In blinded treatment with esomeprazole at 20 mg or placebo for 26 weeks, the former was found to significantly reduce the cumulative proportion of patients developing LDA-induced peptic ulcers (1.1% of patients receiving esomeprazole and 7.4% receiving placebo).[35] Similarly, Yeomans et al reported that 5.4% of patients receiving placebo (n = 27/498) developed LDA-induced peptic ulcers within 26 weeks compared with 1.6% of those receiving esomeprazole 20 mg (1.6%, n = 8/493).[36] Further, Goldstein et al[37] reported that esomeprazole 20 mg was more effective in healing gastric ulcers and better tolerated in 406 patients who needed to continue

Table 2 Pharmacokinetic values for esomeprazole 20 mg in relation to CYP2C19 in Japanese[11]

Dosage regimens	RM	IM	PM
AUC (μmol · hour/L)			
Study 1	3.3 (2.2–5.0)	7.3 (4.7–11.4)	9.2 (7.2–11.8)
Study 2	3.4 (2.5–4.6)	6.0 (4.7–7.7)	1.3 (1.1–1.5)
C_{max} (μmol/L)			
Study 1	1.7 (1.1–2.8)	3.0 (1.9–4.7)	3.3 (2.8–3.8)
Study 2	1.9 (1.5–2.4)	2.4 (2.0–3.0)	2.5 (1.6–3.8)
$t_{1/2}$ (hour)			
Study 1	0.9 (0.7–1.1)	1.3 (1.0–1.7)	1.6 (1.3–1.9)
Study 2	0.9 (0.8–1.1)	1.3 (1.1–1.5)	1.4 (1.1–1.7)

Notes: Maximum plasma concentration (C_{max}; ng/mL), plasma half-life time ($t_{1/2}$; hour), and area under the plasma concentration-time curve (AUC; ng · hour/mL) are given as median values (range).
Abbreviations: RM, rapid metabolizer of CYP2C19; IM, intermediate metabolizer; PM, poor metabolizer.

NSAID therapy (122/138, 88.4%, 95% confidence interval [CI]: 83.1%–93.7%) than ranitidine 150 mg bid (98/132, 74.2%; 95% CI: 66.8%–81.7%). Consequently, in Western populations, an esomeprazole dose of 20 mg appears to reduce the risk of peptic ulcers and symptoms associated with the continuous use of LDA or NSAIDs.

In Japan, esomeprazole at 20 mg od for 4, 12, and 24 weeks in 168 patients treated with NSAIDs (n = 176) prevented the development of peptic ulcers in 99.4% (95% CI: 98.2%–100%), 96.7% (93.8%–99.5%), and 96.0% (92.8%–99.1%), respectively, which are all significantly higher than placebo effects (4 weeks: 78.8%, 95% CI: 72.6%–85.0%; 12 weeks: 69.4%, 95% CI: 62.3%–76.6%; and 24 weeks: 64.4%, 95% CI: 58.6%–71.9%; $P < 0.001$).[11] Further, the preventive effects for NSAIDs-induced peptic ulcers did not depend on the CYP2C19 genotype (96.8% [90.6%–100.0%] in RMs, 95.7% [91.0%–100.0%] in IMs, and 95.8% [90.2%–100.0%] in PMs).[11] Given these findings, esomeprazole 20 mg appears sufficient to reduce the onset of peptic ulcers in Japanese patients using LDA or NSAIDs.

Treatment for GERD

GERD, which often includes an endoscopic mucosal break in the esophagocardial (EC) junction and acid reflux-related symptoms, is a common disease that is estimated to affect around 20%–30% of the population worldwide.[38] In Japan, although the incidence of reflux disease is increasing in Western countries, most Japanese cases of reflux disease are NERD.[39–41] For effective treatment of erosive GERD using acid inhibitory drugs, intragastric pH over a 24-hour period should fall below <4.0 for no longer than 2–4 hours (less than <16.7% of 24 hours).[42] However, we previously demonstrated that LDA-induced esophageal injury prevents or reduces acid inhibition (24-hour intragastric pH >5.0 and pH <4.0 less than 40% of the time) when using a PPI.[43]

In general, esomeprazole is more effective than omeprazole when treating erosive GERD patients.[44,45] A 6-month randomized, double-blind, placebo-controlled trial investigating 375 GERD patients in the United States found respective recovery rates of 78.7%, 54.2%, and 29.1% for patients receiving esomeprazole 20 mg, esomeprazole 10 mg, and a placebo.[46] Although PPI response in patients with NERD is less effective than those with erosive GERD,[47] Chinese patients with NERD showed improved reflux-related symptoms when treated with esomeprazole.[48]

However, other studies have shown that esomeprazole is no more effective than other PPIs when treating GERD. In a multicenter double-blind trial of esomeprazole or omeprazole at 20 mg, the cumulative healing rates at Week 8 in patients with erosive GERD were approximately equal at 90.6% and 88.3%, respectively.[49] In clinical trials comparing rabeprazole 10 mg and esomeprazole 20 mg for NERD in Asian populations, no differences were seen with regard to the primary endpoint of time to achieve a 24-hour symptom-free interval for heartburn (8.5 vs 9 days) or regurgitation (6 vs 7.5 days).[50]

The cumulative healing rates of esomeprazole 20 mg during 4, 12, and 24 weeks for Japanese GERD patients are 97.8% (95% CI: 95.7%–99.9%), 95.0% (91.8%–98.2%), and 92.0% (88.0%–96.0%), respectively.[11] The effect of esomeprazole 20 mg at 24 weeks is significantly higher than esomeprazole 10 mg (82.7%, 95% CI: 77.2%–88.3%; $P = 0.007$).[11]

After oral treatment for 4 weeks with esomeprazole 40 mg, the proportion of RMs, as well as IMs/PMs, is similar between the groups with complete remission and incomplete healing of GERD.[51] Additionally, multivariate analysis showed that the esomeprazole effect is not dependent on the CYP2C19 genotype for complete and incomplete endoscopic healing.

H. pylori eradication therapy in Japan

In Japan, eradication of *H. pylori* is performed for patients with peptic ulcers, mucosa-associate lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, and early gastric cancer resected by endoscopy.[52] The first-line regimen for eradication consists of a PPI administered bid, amoxicillin at 750 mg bid, and clarithromycin at 200 or 400 mg bid for 1 week, while the second-line regimen consists of a PPI bid, amoxicillin at 750 mg bid, and metronidazole at

250 mg bid for 1 week.[53] Major causative factors associated with eradication failure include bacterial resistance to clarithromycin[53] and insufficient gastric acid inhibition during treatment.[4] Indeed, a recent increase in the prevalence of clarithromycin-resistant strains in Japan to more than 30% has been accompanied by a reduction in eradication rates with the clarithromycin-based regimen.[53–55]

Importance of gastric acid inhibition for *H. pylori* eradication

As mentioned above, efforts to eradicate *H. pylori* often fail due to insufficient acid inhibition. Because clarithromycin and amoxicillin are acid-sensitive, acid secretion must be potently inhibited by a PPI to prevent their degradation at low pH.[56] Such potent acid inhibition increases the stability and bioavailability of antibiotics in the stomach and also increases the concentration of antibiotics in gastric mucosa.[57–59] For example, raising the pH from 3.5 to 5.5 increases the in vitro effectiveness of amoxicillin more than 10-fold.[57] Additionally, acid inhibition allows *H. pylori* to reach its growth phase, rendering the bacteria more sensitive to antibiotics.[59]

We previously reported that the pH level over a 24-hour period was significantly higher in patients who achieved successful eradication using lansoprazole plus amoxicillin/clarithromycin as a first line-treatment (6.4 [5.0–7.6]) than those who did not (5.2 [2.2–6.2]), and that when the percent-time for pH $<$ 4 was $<$10% and the 24-hour pH level was $>$6.0, we were able to achieve eradication in a majority of patients, irrespective of the bacterial susceptibility to clarithromycin.[4] As a corollary, when using a PPI/amoxicillin/clarithromycin regimen, the longer the period of elevated pH during treatment, the higher the eradication rates. In our unpublished data, intragastric pH and percent-time of pH $<$ 4 on esomeprazole 20 mg bid in *H. pylori*-negative, healthy young volunteers with high acid secretion were 5.4 (5.2–6.1) and 25.6% (15.0%–31.2%) (Figure 4). These findings strongly suggest that esomeprazole can effectively eradicate *H. pylori* in Japanese populations provided sufficient acid inhibition is achieved.

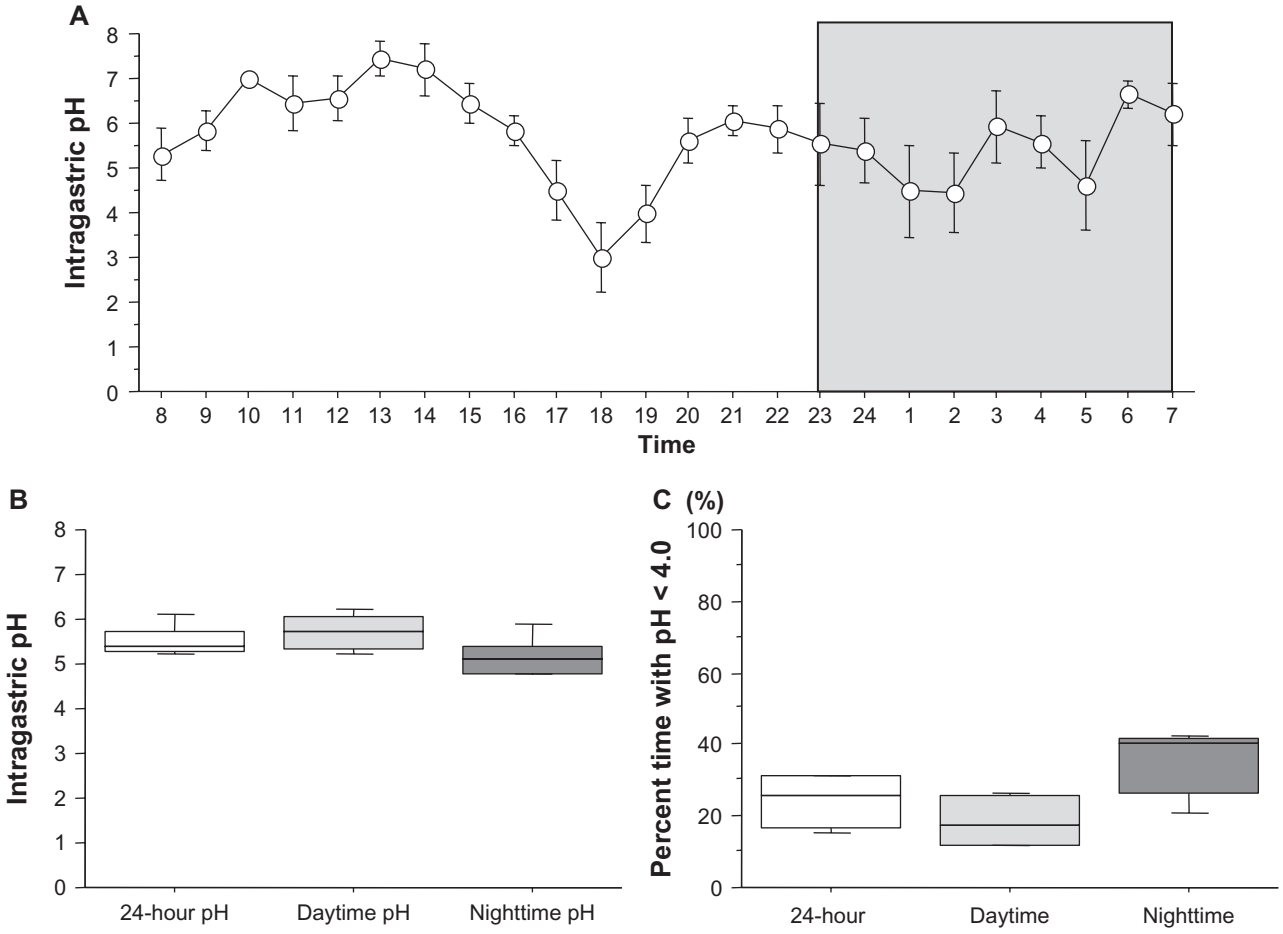

Figure 4 The 24-hour intragastric pH profile (**A**), median intragastric pH value (**B**), and percent time with pH $<$ 4 (**C**) during esomeprazole 20 mg bid treatment for 7 days.

Esomeprazole-based H. pylori eradication therapy

A randomized study from Taiwan shows that the eradication rate when treated with clarithromycin 500 mg, amoxicillin 1 g, and esomeprazole 40 mg bid for 1 week is 86% in the intention-to-treat (ITT) population.[60] First-line *H. pylori* eradication therapy with levofloxacin/amoxicillin plus esomeprazole at 20 mg bid in Chinese patients was 85.2% effective.[61] Further, the eradication rate by ITT analysis was 74.0% with clarithromycin at 500 mg, amoxicillin 1000 mg, and esomeprazole 20 mg bid for 7 days; 78.0% using the same antibiotics plus esomeprazole 40 mg bid for 7 days; and 80.0% for 10 days.[62] That report also suggested that neither esomeprazole dosage nor dosing duration have additive effects on *H. pylori* eradication rates. Although some reports have shown that esomeprazole at 20 mg has an *H. pylori* eradication rate similar to that of omeprazole at 20 mg,[63,64] the rate has also been shown to significantly differ between esomeprazole-based and other PPI-based regimens, such as pantoprazole-based treatment (ITT analysis: 94% vs 82%; $P = 0.009$).[65]

Influence of CYP2C19 polymorphisms on esomeprazole-based *H. pylori* eradication therapy

In Japanese populations, the eradication rates of *H. pylori* by PPI-based eradication therapy differ by CYP2C19 genotype.[66,67] Indeed, eradication rates with triple therapy of PPI bid, amoxicillin 250 mg three times daily (tid), and clarithromycin 200 mg tid for 1 week were 72.7% in RMs, 92.1% in IMs, and 97.8% in PMs.[55] Further, a standard first-line regimen showed eradication rates of 57.7% in RMs, 71.6% in IMs, and 91.7% in PMs.[68] Meta-analysis has shown the absolute risk of genetic differences in eradication failure by PPI-based regimens.[51] Taken together, these reports demonstrate that one reason for the failed eradication by PPI-based therapy is insufficient acid inhibition in CYP2C19 RMs.

However, eradication rates with esomeprazole-based treatment (20 mg and 40 mg bid) have been shown to be independent of CYP2C19 genotype (RM: 87%, IM: 93%, and PM: 92% in one study;[69] and RM: 93%, IM: 93%, and PM: 95% in another).[60] Pan et al[61] reported similar findings using esomeprazole/levofloxacin/amoxicillin in Chinese populations (RM: 82% [41/50], IM: 82% [50/61], and PM: 89% [32/36]). In general, no previous reports have found significant differences in eradication rate for esomeprazole-based treatment among CYP2C19 genotypes.

Interestingly, although eradication rates are significantly higher in esomeprazole-based regimens than omeprazole-based ones (93% vs 76%; $P < 0.05$), this advantage is observed only in RMs.[60] Esomeprazole at 40 mg bid for triple therapy may improve the *H. pylori* eradication compared to omeprazole-based therapy, but likely only in CYP2C19 RMs, as the eradication rates between omeprazole-based and esomeprazole-based regimens are similar in IMs and PMs.[60]

Summary

Compared to omeprazole, esomeprazole is a popular PPI with a better pharmacokinetic profile for the treatment of acid-related diseases, has a higher AUC, and less interindividual variability. However, due to its relatively recent release in Japan, little data are available on its efficacy in Japanese patients. Nevertheless, findings in other populations suggest that esomeprazole will be effective in treating peptic ulcers, GERD, and *H. pylori* in Japanese populations, too.

Because CYP2C19 RM in Japanese is only 30%, which is significantly lower than that in Western population (70%), it is unclear whether this factor means that the clinical results from the treatment of esomeprazole in Japanese are significant. However, this factor cannot ignore acid-related disease, because the prevalence of GERD, NERD, and LDA-related peptic ulcer, which require more potent acid inhibition, is increasing in Japan and a cure rate of GERD and peptic ulcer by PPI treatment differed among Japanese with different CYP2C19 genotype status.[3,70] Further study will be required to increase new knowledge of esomeprazole in Japanese.

Key points

- Esomeprazole is now used as a first-line drug for the treatment of acid-related diseases such as peptic ulcers, GERD, NERD, Zollinger–Ellison syndrome, and *H. pylori* infection in the world.
- Esomeprazole is the first PPI developed as a single isomer, and its metabolism is less dependent on CYP2C19 than CYP3A4 compared to R-omeprazole.
- Although the clearance of esomeprazole is approximately 50% less than omeprazole, the efficacy of esomeprazole on different CYP2C19 genotypes should not be completely ignored.
- CYP2C19 RM patients in particular should be assigned esomeprazole-based treatment against acid-related diseases.
- In Japan, the standard dose of esomeprazole for treatment is 20 mg od, whereas the standard dose in most Western countries is 40 mg od.

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Disclosure

The authors declare they have no conflicts of interest with regard to this work.

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