Original Article

Oral esomeprazole in Japanese pediatric patients with gastric acid-related disease: Safety, efficacy, and pharmacokinetics

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Abstract

Background: Proton pump inhibitors (PPI) are widely used for the treatment of gastric acid-related disease, but they are not approved for use in children in Japan. To assess the safety, pharmacokinetics, pharmacodynamics, and efficacy (gastrointestinal symptom improvement) of PPI in Japanese pediatric patients with gastric acid-related disease, we conducted an 8 week, open-label, parallel-group, multicenter, phase I/III study of once-daily oral esomeprazole use.

Methods: Japanese children, aged 1–14 years with gastric acid-related disease, were stratified by weight and age into five groups (10 patients/group) to receive esomeprazole as granules for suspension (10 mg) or capsules (10 mg or 20 mg) once daily.

Results: Esomeprazole was absorbed and eliminated rapidly in all groups, with a median time to reach maximum plasma concentration of 1.47–1.75 h, an arithmetic mean terminal elimination half-life of 0.80–1.37 h, and a weight-correlated apparent total body clearance of 0.216–0.343 L/h/kg. Area under the plasma concentration-time curve during a dosage interval and maximum plasma drug concentration were generally higher in groups given a higher dose (20 mg) or with a lower age/weight, but also in patients identified as poor metabolizers on cytochrome P450 2C19 genotype. Most patients who had any upper gastrointestinal symptoms at baseline were asymptomatic at the end of the study. Thirty-three patients (66%) reported ≥1 adverse events, including three patients who reported serious adverse events not judged to be causally related to esomeprazole.

Conclusions: Oral esomeprazole, at 10 mg or 20 mg once daily, had a similar safety, efficacy, and pharmacokinetic profile in Japanese pediatric patients to that previously seen in adults and Caucasian children.

Key words: esomeprazole, gastric acid-related disease, Japanese children, pharmacodynamics, pharmacokinetics, safety.

Gastric acid-related disease, such as gastroesophageal reflux disease (GERD), is the most commonly reported type of gastrointestinal (GI) disorder in both adults and children. GERD affects between 10% and 20% of people in the Western world1 and has a prevalence of <10% in Asia.2 The prevalence of GERD is lower in children than in adults, with symptoms of GERD reported in 1–8% of US children;3 this is supported by similar data from Japan.3 There is a consensus that the pathophysiology, clinical course, and manifestation of GERD, including complications such as erosive esophagitis, are similar in adults and children older than 1 year of age.5–7

Proton pump inhibitors (PPI) are the mainstay of treatment for gastric acid-related disease in adults.8 In the Pediatric Gastroesophageal Reflux Clinical Practice Guidelines of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, PPI are recommended as superior to histamine-2 receptor antagonists in relieving symptoms and healing esophagitis.6,9 PPI have been proven to be effective and generally well-tolerated in infants and children.

Esomeprazole, the S-isomer of omeprazole, has been approved for the treatment of GERD in children in more than 75 countries, including the USA, in Europe and in many Asian countries. Esomeprazole is currently approved for use in adults...
only in Japan based on studies demonstrating a strong gastric anti-secretory activity\(^{10}\) and high rates of healing in reflux esophagitis (RE; 87.3%).\(^{11}\)

There is no PPI currently approved for use in children in Japan. The present study investigated the safety, tolerability, clinical efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of esomeprazole in Japanese pediatric patients with gastric acid-related disease.

**Methods**

**Patients**

Study inclusion criteria were as follows: Japanese ethnicity; age, 1–14 years; weight, >10 kg; body mass index 3rd–97th percentile; and confirmed or suspected diagnosis of gastric ulcer (GU), duodenal ulcer (DU), anastomotic ulcer (AU), non-erosive reflux disease (NERD), RE, or Zollinger–Ellison syndrome, based on upper GI endoscopy, pH monitoring, and/or clinical symptoms.

Patients were excluded if they had been significantly ill or had taken any PPI in the last 4 weeks. Patients who had a condition deemed to interfere with the study, had allergy to PPI, or a requirement for medication that could interact with esomeprazole were also excluded. Patients were free to withdraw from the study at any time, or could be withdrawn by their guardians or the investigators.

**Ethics approval**

The study was conducted in accordance with the ethics principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, Good Clinical Practice for Trials on Drugs (Ministry of Healthy, Labor and Welfare (MHLW) Ordinance No. 28, 27 March 1997), and applicable regulatory requirements. Written, informed consent was obtained from the guardians of all patients before enrolment in the study. Additional consent was obtained for intragastric pH monitoring and esophagogastro-duodenoscopy (EGD). The study protocol was approved by the institutional review board at each participating site. The study was registered at ClinicalTrials.gov (NCT02153398).

**Study design**

This study was conducted between June 2014 and April 2016 at 20 Japanese pediatric sites.

This open-label, parallel-group, combined phase I/III clinical study was conducted to determine the safety and efficacy of esomeprazole in Japanese pediatric patients with gastric acid-related disease. The study involved five scheduled visits: enrolment; registration; and visits after 1, 4, and 8 weeks of dosing. PK and upper GI symptoms were assessed in all patients but intragastric pH and EGD were performed only in the subset of patients who gave consent for these investigations.

The patients were allocated to five groups based on age and bodyweight, to receive esomeprazole for 8 weeks. Patients <20 kg were allocated to group 1 and received a 10 mg esomeprazole sachet daily. Patients ≥20 kg were randomized to groups 2–5, based on their age (1–11 or 12–14 years old) and given either 10 mg (groups 2 and 4) or 20 mg (groups 3 and 5) esomeprazole once daily in capsule form (Fig. 1). The sample size was based on feasibility to include at least 10 each in groups 2–5 (i.e. 40 patients in total), and 5–10 patients in group 1.

The esomeprazole doses in this study were based on US/EU approved doses and on PK, safety and clinical data from previous pediatric studies in Caucasian subjects that demonstrated relevant exposure following 10 and 20 mg, but too low exposure following a dose of 5 mg.\(^{12–16}\) Bioequivalence has previously been demonstrated between esomeprazole given as sachets (granules for suspension) and capsules (Dr Helen Lunde, unpubl. data, 2014).

**Safety and tolerability**

Safety and tolerability were evaluated on adverse events (AE), physical examination, vital signs, and clinical laboratory tests. AE were recorded from registration until last visit or withdrawal. Serious AE (SAE), however, were recorded from the time of informed consent, at enrolment.

\[\text{Fig. 1} \quad \text{Study flow chart.}\]
Blood and urine samples for clinical chemistry, hematol-
ogy, and urinalysis were collected after ≥4 h of fasting. All
patients who received at least one dose of esomeprazole
and had any post-dose data were included in the safety
analysis.

Upper GI symptoms

The intensity of the upper GI symptoms, that is, heartburn,
epigastric pain, upper abdominal discomfort, and regurgitation,
were recorded at baseline and then daily during treatment by
the patient/guardians, and at baseline and after 1, 4, and
8 weeks of treatment by the investigators. Baseline recording
was performed at registration, based on a 7-day retrospective
evaluation. Symptom intensity was scored as 0, no symptoms,
“none”; 1, easily tolerated, “mild”; 2, interference with normal
activities, “moderate”; and 3, not able to perform normal
activities, “severe”.

Pharmacokinetics, Helicobacter pylori

Pharmacokinetic evaluation was performed after ≥5 days of
repeated dosing, with participants fasted for ≥4 h before and
until 1 h after dosing. Blood sampling was performed 30 min
before (trough concentration) and 30, 60, 90, 120, 180, 240,
and 360 min after dosing. Blood samples were spun at
≥2,000 × g for 20 min at 4°C to obtain plasma samples and
stored at ≤−20°C until analyzed using a validated bioanalytical
method by Covance Laboratories Limited (Harrogate, UK).

The following PK variables were analyzed: area under the
plasma concentration–time curve (AUC) during a dosage interval
(AUC_{\text{tau}}); AUC from time zero to time t (AUC_{0–t}); maximum
plasma drug concentration (C_{\text{max}}); time to reach maximum plasma concentration (t_{\text{max}}); terminal elimination
half-life (t_{1/2}); apparent total body clearance (CL/F); and
apparent volume of distribution during terminal phase after
non-i.v. administration (V_{\text{f}}/F).

The PK variables of 5-hydroxy and sulfone metabolites
of esomeprazole were also assessed and included AUC_{\text{tau}},
AUC_{0–t}, C_{\text{max}}, t_{\text{max}}, and t_{1/2}. Concentration–time data were
analyzed using a non-compartmental approach with
WinNonlin Enterprise Edition version 5.2.1 (Pharsight,
MountainView, CA, USA). The PK data analysis set
included all patients who had at least one recorded plasma
concentration after dosing and had no protocol deviations
with impact on the PK.

Blood sampling for genotyping of CYP2C19, encoding a
metabolizing enzyme of esomeprazole, was, after informed
consent, obtained from all participants at enrolment Genetic
testing was conducted by LSI Medience (Tokyo, Japan).
CYP2C19 single-nucleotide polymorphisms (SNP) resulting in
point mutations of 681G>A (*2) and 636G>A (*3) were
detected and the SNP genotypes were translated into star-allele
genotypes. The patients were classified as homo-extensive
metabolizers (homo-EM) (*1/*1), hetero-EM (*1/*2, *1/*3)
and poor metabolizers (PM) (*2/*2, *2/*3, *3/*3).

All patients were tested for H. pylori immunoglobulin G
antibodies in the blood, according to each institution’s stan-
dard method.

Intragastric pH, EGD

Intragastric pH monitoring, to assess PD of esomeprazole, was
performed at baseline (data not demonstrated) and after
≥5 days of repeated dosing in the subgroup of patients who
gave consent for this investigation. The participants fasted for
≥4 h before pH monitoring, a standardized diet with a pH
between 5 and 7 was given during the test period. A nasal pH
probe was inserted into the stomach and location confirmed
on X-ray. Intragastric pH was recorded every 10 s for 12 h.
The PD analysis set included all patients who had baseline
and post-baseline PD data without any protocol deviations
with impact on the PD. The percentage of time with intragastric
pH >4 and >3, and the median intragastric pH for 12 h
were analyzed. EGD assessment was performed in patients
who gave consent for this evaluation, at baseline (including
EDG in the 2 weeks before registration) and if clinically indi-
cated during the treatment period.

Statistical analysis

Clinical laboratory data and vital signs are presented by treat-
ment group as descriptive statistics for count, mean, standard
deviation, maximum, median, and minimum at baseline and
subsequent visits, and changes from baseline. Qualitative data
are summarized for each treatment by frequency and percent-
age. Changes from baseline to last visit are presented in shift
tables showing distribution of patients with values below and
above the reference range compared with pre- and post-treat-
ment values. Baseline values were from visit 1, and for clinical
laboratory data and vital signs at visit 2.

No hypothesis tests were used, a two-sided 0.05 level of
significance was used for assessing confidence intervals. All
statistical analyses were performed using SAS version 9.3
(SAS Institute, Cary, NC, USA).

Results

Patients

Fifty-five patients were screened, of whom 50 (female, 52%)
were eligible and registered in the study into five treatment
groups (10 patients per group); all registered patients received
esomeprazole, and 47 completed the study; one discontinued
due to an AE and two due to withdrawal of consent. Median
exposure to esomeprazole was similar in the five groups, and
ranged across the groups from 55.0 days to 56.5 days.

The most frequently reported eligible diseases were NERD,
with six patients each (60%) in groups 1, 3, and 4; RE, with
five patients (50%) in group 2; and GU, with five patients
(50%) in group 5. Some patients had more than one diagnosis.
In total, five patients (10%) tested positive for H. pylori, two

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Table 1 Demographic and baseline participant characteristic

| Demographic characteristics | Esomeprazole groups | Total |
|-----------------------------|---------------------|-------|
| Sex (female)                | Group 1 (n = 10)    | Group 2 (n = 10) | Group 3 (n = 10) | Group 4 (n = 10) | Group 5 (n = 10) | (n = 50) |
| Age (years)†                | 5 (50)              | 6 (60)              | 2 (20)              | 7 (70)              | 6 (60)              | 26 (52) |
| Weight (kg)†                | 14.2 ± 3.1          | 28.9 ± 6.1          | 27.3 ± 6.1          | 51.0 ± 8.1          | 51.9 ± 6.1          | 33.6 ± 15.0 |
| Gastric ulcer†              | 2 (20)              | 1 (10)              | 2 (20)              | 2 (20)              | 4 (40)              | 5 (10) |
| Duodenal ulcer†             | 1 (10)              | 4 (40)              | 6 (60)              | 6 (60)              | 4 (40)              | 29 (58) |
| NERD†                       | 6 (60)              | 4 (40)              | 6 (60)              | 6 (60)              | 4 (40)              | 11 (22) |
| Reflux esophagitis†         | 1 (10)              | 5 (50)              | 0 (0)               | 2 (20)              | 3 (30)              | 14 (28) |
| _Helicobacter pylori_ (IgG antibody) | 2 (20)              | 1 (10)              | 1 (10)              | 0 (0)               | 1 (10)              | 7 (14) |
| CYP2C19 genotype            | Homo-EM             | 4 (40)              | 1 (10)              | 0 (0)               | 4 (40)              | 5 (10) |
|                             | Hetero-EM           | 4 (40)              | 7 (70)              | 9 (90)              | 4 (40)              | 5 (10) |
|                             | PM                  | 2 (20)              | 2 (20)              | 1 (10)              | 2 (20)              | 0 (0) |

† At enrolment. ‡ Some subjects had overlapping diagnoses of gastric ulcer, duodenal ulcer, NERD, and reflux esophagitis. Group 1, age ≥1 year, weight <20 kg, esomeprazole sachet 10 mg; group 2, age 1–11 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 3, age 1–11 years, weight ≥20 kg, esomeprazole capsule 20 mg; group 4, age 12–14 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 5, age 12–14 years, weight ≥20 kg, esomeprazole capsule 20 mg. EM, extensive metabolizer; NERD, non-erosive reflux disease; PM, poor metabolizer.

Table 2 Adverse events reported by two patients or more

| Patients with any adverse event, n (%) | Group 1 (n = 10) | Group 2 (n = 10) | Group 3 (n = 10) | Group 4 (n = 10) | Group 5 (n = 10) | Total (n = 50) |
|---------------------------------------|------------------|------------------|------------------|------------------|------------------|----------------|
| Nasopharyngitis                       | 1 (10)           | 4 (40)           | 2 (20)           | 1 (10)           | 3 (30)           | 11 (22)        |
| Upper respiratory tract infection     | 1 (10)           | 1 (10)           | 0 (0)            | 1 (10)           | 0 (0)            | 3 (6)          |
| Gastroenteritis                       | 1 (10)           | 0 (0)            | 0 (0)            | 0 (0)            | 1 (10)           | 2 (4)          |
| Pneumonia                             | 2 (20)           | 0 (0)            | 0 (0)            | 0 (0)            | 0 (0)            | 2 (4)          |
| Diarrhea                              | 1 (10)           | 0 (0)            | 2 (20)           | 0 (0)            | 1 (10)           | 4 (8)          |
| Nausea                                | 0 (0)            | 1 (10)           | 0 (0)            | 0 (0)            | 2 (20)           | 3 (6)          |
| Abdominal pain                        | 0 (0)            | 0 (0)            | 1 (10)           | 0 (0)            | 1 (10)           | 2 (4)          |
| Vomiting                              | 2 (20)           | 0 (0)            | 0 (0)            | 0 (0)            | 0 (0)            | 2 (4)          |
| Headache                              | 0 (0)            | 2 (20)           | 0 (0)            | 0 (0)            | 2 (20)           | 4 (8)          |
| Upper respiratory tract inflammation  | 0 (0)            | 1 (10)           | 0 (0)            | 1 (10)           | 0 (0)            | 2 (4)          |

Group 1, age ≥1 year, weight <20 kg, esomeprazole sachet 10 mg; group 2, age 1–11 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 3, age 1–11 years, weight ≥20 kg, esomeprazole capsule 20 mg; group 4, age 12–14 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 5, age 12–14 years, weight ≥20 kg, esomeprazole capsule 20 mg.

Safety and tolerability

Of the 50 patients assessed for safety, 33 patients (66.0%) reported one or more AE during the study period, nasopharyngitis (22.0%) being the most frequent (Table 2). The AE were scored as mild/moderate in 31/33 patients. Three events (abdominal pain, diarrhea, and photosensitivity reaction) in two patients (4.0%) were judged to be causally related to esomeprazole. Although no causality of esomeprazole was reported, three patients (two in group 1 and one in group 5) had one SAE each (anaphylactic reaction to milk, irritable bowel syndrome, and aggravation of known asthma, the latter [group 1] leading to withdrawal of consent). Esomeprazole was discontinued in one patient in group 3 due to AE (abdominal pain and diarrhea). There were no deaths during the study period.

No clinically relevant trends were observed during the study in either blood or urine laboratory or physical examinations.

Upper GI symptoms

Upper GI symptoms were recorded in all 50 patients, with approximately half of the patients having upper GI symptoms
at baseline (time of registration). In patients who had any symptoms at baseline, however, most patients (in all groups) became asymptomatic and reached sustained resolution (7 consecutive days free of symptoms) for all symptoms at the end of the study (Table 3). The investigator assessments of upper GI symptoms were generally in line with those recorded by the patients/guardians (data not shown).

**Pharmacokinetics**

Pharmacokinetics were analyzed in all registered patients, except for two patients for whom no blood samples were obtained \((n = 48)\). The PK variables and plasma concentration–time curves obtained for esomeprazole are summarized in Table 4 and Figure 2, respectively.

Esomeprazole was absorbed and eliminated rapidly in all groups, with a median \(t_{\text{max}}\) of 1.47–1.75 h, an arithmetic mean \(t_{1/2}\) of 0.80–1.37 h, and a weight-correlated CL/F of 0.216–0.343 L/h/kg. Even if high inter-individual variability was observed, in general, the \(\text{AUC}_{\text{tau}}\) and \(C_{\text{max}}\) were greater at the higher dose (20 mg) in patients with lower age and weight.

As expected, geometric mean for exposure was highest in patients lacking \(CYP2C19\) activity (PM), whereas the lowest mean exposure was observed in patients with the highest activity of \(CYP2C19\) (homo-EM). Due to high inter-individual variability, however, some PM patients had lower exposure than EM patients in the same dosing group (Table 4).

The ratio of hydroxy and sulfone metabolite to esomeprazole for \(\text{AUC}_{\text{tau}}\) and \(C_{\text{max}}\) were in line with and confirmed the total \(\text{AUC}_{\text{tau}}\) and \(C_{\text{max}}\) results for the different \(CYP2C19\) genotyping groups (Table 5).

**Intragastric pH**

In this study, intragastric pH analysis was done in a subgroup of five patients who consented to this evaluation and for whom PD data were made available (two in group 2 and group 3, one in group 5). After \(\geq 5\) days of esomeprazole dosing, the percentage of time with intragastric pH \(>4\) was from 51.2% to 98.3% and the percentage of time with intragastric pH \(>3\) was from 65.4% to 99.0%.

**Endoscopy**

Esophagogastroduodenoscopy was performed in a subgroup of 14 patients who consented to this evaluation. At baseline, two patients were identified to have DU and one, RE on endoscopy; all resolved after esomeprazole treatment. Lesions were not detected on endoscopy at baseline in the other 11 patients. Of these, 10 patients were comprehensively

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**Table 3** Maximum intensity of upper GI symptom according to patient diary (FAS)

| Upper GI symptoms | Time point | Maximum intensity | Esomeprazole group |
|-------------------|------------|-------------------|--------------------|
|                   | Group 1 \((n = 10)\) | Group 2 \((n = 10)\) | Group 3 \((n = 10)\) | Group 4 \((n = 10)\) | Group 5 \((n = 10)\) |
|                   | \(n (%)\) | \(n (%)\) | \(n (%)\) | \(n (%)\) | \(n (%)\) |
| Heartburn         | Baseline | None | 8 (80) | 7 (70) | 9 (90) | 8 (80) | 6 (60) |
|                   | Mild     | 1 (10) | 2 (20) | 1 (10) | 2 (20) | 2 (20) |
|                   | Moderate or severe | 1 (10) | 1 (10) | 0 (0) | 0 (0) | 2 (20) |
|                   | Week 8 | None | 9 (100) | 7 (70) | 8 (89) | 9 (100) | 9 (90) |
|                   | Mild | 0 (0) | 3 (30) | 1 (11) | 0 (0) | 1 (10) |
|                   | Moderate or severe | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Epigastric pain   | Baseline | None | 8 (80) | 4 (40) | 4 (40) | 5 (50) | 3 (30) |
|                   | Mild | 2 (20) | 3 (30) | 5 (50) | 2 (20) | 2 (20) |
|                   | Moderate or severe | 0 (0) | 3 (30) | 1 (10) | 3 (30) | 5 (50) |
|                   | Week 8 | None | 9 (100) | 7 (70) | 8 (89) | 5 (56) | 5 (50) |
|                   | Mild | 0 (0) | 2 (20) | 1 (11) | 3 (33) | 2 (20) |
|                   | Moderate or severe | 0 (0) | 1 (10) | 0 (0) | 1 (11) | 3 (30) |
| Upper abdominal discomfort | Baseline | None | 7 (70) | 4 (40) | 6 (60) | 5 (50) | 4 (40) |
|                   | Mild | 3 (30) | 3 (30) | 2 (20) | 3 (30) | 3 (30) |
|                   | Moderate or severe | 0 (0) | 3 (30) | 2 (20) | 2 (20) | 3 (30) |
|                   | Week 8 | None | 9 (100) | 6 (60) | 7 (78) | 6 (67) | 6 (60) |
|                   | Mild | 0 (0) | 4 (40) | 2 (22) | 2 (22) | 1 (10) |
|                   | Moderate or severe | 0 (0) | 0 (0) | 0 (0) | 1 (11) | 3 (30) |
| Regurgitation     | Baseline | None | 6 (60) | 7 (70) | 5 (50) | 6 (60) | 6 (60) |
|                   | Mild | 3 (30) | 3 (30) | 4 (40) | 4 (40) | 2 (20) |
|                   | Moderate or severe | 1 (10) | 0 (0) | 1 (10) | 0 (0) | 2 (20) |
|                   | Week 8 | None | 6 (67) | 9 (90) | 6 (67) | 8 (89) | 10 (100) |
|                   | Mild | 3 (33) | 1 (10) | 3 (33) | 0 (0) | 0 (0) |
|                   | Moderate or severe | 0 (0) | 0 (0) | 0 (0) | 1 (11.1) | 0 (0) |

Group 1, age \(\geq 1\) year, weight \(< 20\) kg, esomeprazole sachet 10 mg; group 2: age 1–11 years, weight \(\geq 20\) kg, esomeprazole capsule 10 mg; group 3, age 1–11 years, weight \(\geq 20\) kg, esomeprazole capsule 20 mg; group 4, age 12–14 years, weight \(\geq 20\) kg, esomeprazole capsule 10 mg; group 5, age 12–14 years, weight \(\geq 20\) kg, esomeprazole capsule 20 mg. FAS, full-analysis set; GI, gastrointestinal.
Table 4 Esomeprazole PK parameters vs dose (PK analysis set, 48 patients)

| Esomeprazole dose group | Group 1 (n = 9) | Group 2 (n = 10) | Group 3 (n = 10) | Group 4 (n = 9) | Group 5 (n = 10) |
|-------------------------|----------------|----------------|----------------|----------------|----------------|
| AUCtau (µmol/h/L)†       | 6.54 (42.6%)†† | 2.88 (78.3%)‡  | 10.0 (50.9%)    | 1.79 (105.5%)  | 5.55 (33.6%)   |
| AUC0-τ (µmol/h/L)†       | 4.04 (126.7%) | 2.34 (99.2%)   | 9.53 (47.8%)    | 1.56 (100.0%)  | 5.20 (33.6%)   |
| Cmax (µmol/L)†           | 2.47 (141.7%) | 1.55 (110.4%)  | 5.52 (41.5%)    | 0.899 (91.7%)  | 2.84 (51.3%)   |
| tmax (h)‡                | 1.58 (1.03–5.92) | 1.52 (0.92–6.00) | 1.47 (0.93–1.52) | 1.57 (0.93–2.95) | 1.75 (0.95–3.00) |
| t1/2 (h)§                | 0.80 ± 0.18‡‡  | 0.97 ± 0.55‡‡  | 1.08 ± 0.44     | 1.37 ± 0.88    | 1.06 ± 0.25    |
| CL/F (L/h)               | 4.42 (42.6%)†† | 10.0 (78.3%)‡‡ | 5.78 (50.9%)    | 16.2 (105.5%)  | 10.4 (33.6%)   |
| Weight-corrected CL/F (L/h/kg) | 0.315 (53.7%)‡† | 0.343 (58.7%)‡‡ | 0.216 (40.4%)   | 0.316 (109.6%) | 0.227 (45.9%)  |

†Geometric mean (coefficient of variation); ‡arithmetic mean ± SD; §median (range); †geometric mean (no. patients). ††n = 7; ‡‡n = 9.

Group 1, age ≥1 year, weight <20 kg, esomeprazole sachet 10 mg; group 2: age 1–11 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 3, age 1–11 years, weight ≥20 kg, esomeprazole capsule 20 mg; group 4, age 12–14 years, weight ≥20 kg, esomeprazole capsule 10 mg; group 5, age 12–14 years, weight ≥20 kg, esomeprazole capsule 20 mg. AUC0–τ, under the plasma concentration–time curve from time 0 to time t; AUCtau, under the plasma concentration–time curve during a dosage interval; Cmax, maximum plasma drug concentration; CL/F, apparent total body clearance; EM, extensive metabolizer; PK, pharmacokinetics; PM, poor metabolizer; t1/2, terminal elimination half-life; tmax, time to reach maximum plasma concentration.

In general, the AE reported were low in intensity and had a frequency in line with expectations. Two patients had mild/moderate AE judged to be causally related to the study drug, and three patients had SAE not causally related to the study drug.

The safety of 10 or 20 mg esomeprazole, given once daily as capsules or sachets for 8 weeks, was considered acceptable for all study groups and in line with the safety profile from previous studies in Caucasian children and in Japanese adults.10–15

Score of upper GI symptoms was collected throughout the study. Even if a limited number of patients reported symptoms during 7 days preceding the registration visit, most patients who reported symptoms at baseline became asymptomatic during treatment. Almost all patients had no or only mild symptoms at the end of the study, which was generally consistent with previous studies in Caucasian children and in Japanese adults.10–15

Three patients with endoscopically verified DU or RE at baseline had complete resolution following treatment with esomeprazole. Even if limited, however, these clinical findings suggest that esomeprazole has a clinically beneficial effect in Japanese children, as has been demonstrated in adult Japanese10,11 and Western pediatric patients.12,13

The PK variables for esomeprazole indicated rapid absorption and elimination in Japanese children. The inter-individual variabilities in exposure were high even in the same age/weight/dose groups. Mean plasma concentration was higher in younger children, but the increase in CL/F seen in younger patients disappeared when normalized to bodyweight. In general, the exposure increased more than proportionately with an increase in dose, from 10 mg to 20 mg. The inter-individual variability, as well as the age, weight and dose dependency are all consistent with previous findings in Japanese adults, and in Caucasian children.10,14,15,17 The more pronounced variability in children may

Fig. 2 Plasma concentration–time curve for esomeprazole for (●) group 1, age ≥1 year, weight <20 kg, esomeprazole sachet 10 mg; (●●) group 2, age 1–11 years, weight ≥20 kg, esomeprazole capsule 10 mg; (●●) group 3, age 1–11 years, weight ≥20 kg, esomeprazole capsule 20 mg; (●●●) group 4, age 12–14 years, weight ≥20 kg, esomeprazole capsule 10 mg; (●●●) group 5, age 12–14 years, weight ≥20 kg, esomeprazole capsule 20 mg. Data given as arithmetic mean ± SD. Pharmacokinetics analysis set.

diagnosed with NERD, and one with DU, based on endoscopy performed before registration and the development of clinical symptoms.

Discussion

This is the first study examining the effect of esomeprazole on safety and tolerability, clinical efficacy, PK, and PD in Japanese pediatric patients aged 1–14 years with gastric acid-related disease.
be partly explained by the lower number of plasma samples in children, potential loss of substance/dose due to spitting/vomiting in some smaller children, and, further, the age-dependent maturation of the \textit{CYP} liver enzymes.\textsuperscript{17}

Omeprazole and esomeprazole are metabolized mainly by the enzymes \textit{CYP}3A4 and \textit{CYP}2C19;\textsuperscript{18} the latter exists in several different functional genotypes. Patients with homozygous non-functional \textit{CYP}2C19 alleles are PM and have higher exposure to omeprazole, and, to a lesser extent, esomeprazole, compared with patients with homozygous-active \textit{CYP}2C19 alleles (homo-EM) or heterozygous-active/non-functional \textit{CYP}2C19 alleles (hetero-EM). Despite the differences in exposure due to \textit{CYP}2C19 genotype, no differences have been seen in safety profile between PM and EM.\textsuperscript{19–21}

The prevalence of PM is known to be higher in East Asian populations than in Caucasian populations.\textsuperscript{22} When patients are stratified by PM/EM, however, there are no differences in exposure to omeprazole or esomeprazole between the two geographical regions (Dr Per Lundborg, unpubl. data, 2004). In this study, the exposure in PM Japanese children was generally higher than that in EM children, even if the overlap due to inter-individual variability is large. Overall, Japanese and non-Japanese children receiving 10 mg or 20 mg esomeprazole have similar PK profiles.\textsuperscript{14,15}

In this study, assessment of PD variables using intragastric pH monitoring was performed in a subgroup of Japanese children. Although the number of patients who consented to intragastric pH monitoring was small, a longer duration of gastric pH \( \geq 4 \) with esomeprazole treatment was indicated, as has been seen in previous studies in Japanese adults (Dr Per Lundborg, unpubl. data, 2004) and Caucasian children.\textsuperscript{17}

The limitations of this pediatric study include the small sample size and, especially, the low number of patients evaluated for changes in symptoms, EGD, and intra-gastric pH. The relatively large pediatric population for PK evaluation and the combined evaluation of safety, clinical efficacy, PK, and PD, however, partially offset the limitations and enabled us to make reasonable assessments, supported by previous studies in Japanese adults and Caucasian children. Due to the recognized complexity of pediatric studies, it is standard for the clinical significance of pediatric data to be comprehensively assessed not only using standard statistical methods, but also with observations supported and supplemented by similar studies in adults in the same indication.\textsuperscript{23}

In conclusion, in Japanese pediatric patients aged 1–14 years with gastric acid-related disease, treatment with esomeprazole capsules or sachets at 10 mg or 20 mg once daily for 8 weeks produced no new safety concerns. The study drug was generally well tolerated and the present results are supported by the previous, well documented safety profiles in Japanese adults and Caucasian children. The PK profile involved age/weight, PM/EM, and dose-dependent exposure of esomeprazole. The efficacy was supported by the resolution of both upper GI symptoms and EGD. Esomeprazole had a similar PK, efficacy, and safety profile in Japanese children as previously seen in Caucasian children and Japanese in adults.

Table 5 Exposure to esomeprazole and hydroxy and sulfone metabolites (PK analysis set)

| Group | \textit{CYP}2C19 genotype | \textit{n} | Esomeprazole (A) | Hydroxy metabolite (B) | Sulfone metabolite | Ratio of metabolite |
|-------|--------------------------|-----------|-----------------|---------------------|-----------------|-------------------|
|       |                          |           | \( \text{AUC}\text{\_}\text{\_\_tau} \) | \( \text{C}\text{\_\_max} \) | \( \text{AUC}\text{\_\_tau} \) | \( \text{C}\text{\_\_max} \) | \( \text{AUC}\text{\_\_tau} \) | \( \text{C}\text{\_\_max} \) |
|       |                          |           | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} | (\text{\text{\( \text{\( \mu\text{mol/L} \))\)}} |
| 1     | Homo-EM                  | 3         | 5.47            | 4.56                | 0.589           | 0.414             | 7.50             | 1.40             | 0.11             | 0.09             | 1.37             | 0.31             |
| 2     | Homo-EM                  | 1         | 1.17            | 0.989               | 0.246           | 0.126             | 0.833            | 0.346            | 0.21             | 0.13             | 0.71             | 0.35             |
| 3     | Homo-EM                  | 2         | 6.71            | 4.62                | 0.319           | 0.178             | 20.6             | 2.38             | 0.05             | 0.04             | 3.07             | 0.51             |
| 4     | Homo-EM                  | 4         | 6.36\textsuperscript{1} | 1.16               | 0.496\textsuperscript{1} | 0.094            | 8.73\textsuperscript{1} | 0.575            | 0.08             | 0.08             | 1.37             | 0.50             |
| 5     | Homo-EM                  | 2         | 8.82            | 4.51                | 0.449           | 0.191             | 21.5             | 2.33             | 0.05             | 0.04             | 2.44             | 0.52             |
| 6     | Hetero-EM                | 7         | 2.35\textsuperscript{2} | 1.21               | 0.368\textsuperscript{3} | 0.124            | 3.69\textsuperscript{11} | 0.475            | 0.15             | 0.10             | 1.46             | 0.39             |

\( \text{n} = 2 \); \( \text{n} = 6 \); \( \text{n} = 4 \); \( \text{n} = 3 \); \( \text{n} = 1 \); \( \text{n} = 8 \). Group 1, age \( \geq 1 \) year, weight \( < 20 \) kg, esomeprazole sachet 10 mg; group 2: age 1–11 years, weight \( \geq 20 \) kg, esomeprazole capsule 10 mg; group 3, age 1–11 years, weight \( \geq 20 \) kg, esomeprazole capsule 20 mg; group 4, age 12–14 years, weight \( \geq 20 \) kg, esomeprazole capsule 10 mg; group 5, age 12–14 years, weight \( \geq 20 \) kg, esomeprazole capsule 20 mg. \( \text{AUC}\text{\_\_tau} \) under the plasma concentration–time curve during a dosage interval; \( \text{C}\text{\_\_max} \), maximum plasma drug concentration; EM, extensive metabolizer; PK, pharmacokinetics; PM, poor metabolizer.
Based on the present data, the MHLW-approved dosing for Japanese children 1–14 years is as follows: (i) reflux esophagitis, gastric or duodenal ulcer and Zollinger–Ellison syndrome: <20 kg bodyweight, 10 mg oral dose; >20 kg bodyweight, 10–20 mg oral dose; and for (ii) non-erosive esophagitis, 10 mg oral dose.

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Author contributions

T.Sh., H.R. and T.Y. contributed to the conception/design of this study and evaluation of the results; Y.N. contributed to the design of this study, data collection and analysis; E.I., S.I., T.Sa., D.T. and K.A. contributed to the data collection and analysis; M.N. contributed to the statistical analysis and evaluation of the results. All authors read and approved the final manuscript.

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