Acid-suppressive effects of generic omeprazole: Comparison of three brands of generic omeprazole with original omeprazole

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Conflict of interest statement

None declared.

Abstract

Background. Generic omeprazole contains the same active ingredient as original omeprazole and require verification of the bioequivalence with original omeprazole. However, very few clinical studies have been reported.

Aims. A prospective, randomized, open-label, crossover study to compare acid-suppressive effect of generic omeprazole with that of original omeprazole.

Subjects. Seven healthy *Helicobacter pylori*-negative subjects of CYP2C19 extensive metabolizer.

Methods. Intragastric pH was measured for 24-h without medications (placebo) and on day 7 of repeated administration of 10 mg once daily after breakfast of original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap.

Results. Median values of intragastric pH and percentages of time with pH > 4 for 24-h were significantly higher with administration of any omeprazole formulation compared with placebo ($P < 0.05$, Wilcoxon signed-rank test). Whereas, during the night-time period (20:00-08:00 h), percentages of time with pH > 4 with Omeprazole-Towa and Omerap were not significantly higher than placebo. Compared with Omeprazon, these two parameters for 24-h showed significantly greater inter-subject variations with Omeprazole-Towa ($P < 0.05$ and $P < 0.01$, F-test) and Ovulanze ($P < 0.05$).

Conclusions. Acid-suppressive effects of some brands of generic omeprazole are not the same as original omeprazole. These differences might be reflected in clinical outcomes.

Keywords: Generic product, Intragastric pH, Omeprazole

1. Introduction

Proton pump inhibitors (PPIs), such as omeprazole, lansoprazole and rabeprazole, are considered to have stronger gastric acid-suppressive effects than histamine H_2 receptor antagonists [1–4], and are widely used in initial and maintenance therapy for gastroesophageal reflux disease (GERD).

Recently, it has been found that cytochrome P450 2C19 (CYP2C19), which is a major enzyme involved in PPI metabolism [5], has three hereditary genotypes: homozygous extensive metabolizers with higher enzymatic activity, heterozygous extensive metabolizers with moderate enzymatic activity, and poor metabolizers with markedly impaired enzyme activity [6–9]. Therefore, a subject's CYP2C19 genotype affects the acid-suppressive effects of PPIs, and differences in its effects among the three genotypic groups are significant [10–15]. As a result, the acid-suppressive effect of PPIs should be studied in relation to CYP2C19 genotype status.

In Japan, as well as many other countries, in an effort to reduce medical expenditure, the authorities have recently been promoting the use of generic drugs which contain the same active ingredients as the original products, and this may involve verifying the stability, quality and effects of the generic drugs. However, in terms of volume of all prescriptions, generic products accounted for only 11% in Japan, but 54% in the United States, 52% in the United Kingdom, and 54% in Germany in 2001 [16].

Since 2004, an increasing number of generic omeprazole-containing products have been on the market in Japan. Studies to determine the bioequivalence between original and generic omeprazole have been performed [17-19], however, most of them did not take account of CYP2C19 genotypic status [18, 19]. Therefore, it is difficult to assess whether each generic omeprazole formulation exhibits exactly the same pattern of drug

absorption as original omeprazole. Moreover, questions of therapeutic equivalence can also be raised.

The aim of this study was to compare the acid-suppressive effects of 10 mg of three brands of generic omeprazole recently available in Japan, as test products, with original omeprazole, as a reference product, in CYP2C19 extensive metabolizers without *Helicobacter pylori* (*H. pylori*) infection.

2. Materials and methods

2.1. Subjects

Seven healthy Japanese subjects (six males and one female) who were *H. pylori*-negative CYP2C19 extensive metabolizers (five homozygous extensive metabolizers and two heterozygous extensive metabolizers) participated in this study. The subjects, aged 22–33 years (median 24 years) and weighing 55–95 kg (median 67 kg), had no history of gastrointestinal or hepatobiliary disease, or of eradication therapy for *H. pylori*, and took no regular medications. The full medical history of each subject was recorded and each received a physical examination.

2.2. H. pylori infection

H. pylori infection was determined by measuring the serum titer of IgG antibodies to *H. pylori* by an enzyme immunoassay (HM-CAP Kit, Enteric Products, NY, USA), and by the ^{13}C-urea breath test (UBT). Only subjects negative to both tests were considered to be free from *H. pylori* infection.

2.3. CYP2C19 genotyping

Genotyping procedures identifying the *CYP2C19*1* wild-type gene and the two mutated alleles, *CYP2C19*2* in exon 5 and *CYP2C19*3* in exon 4, were performed by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, originally described by de Morais *et al*. [20, 21], with minor modifications as reported by Kubota *et al*. [8], at the laboratory center at SRL, Tokyo, Japan. Genotypic status was determined by the existence of *CYP2C19*2* in exon 5 and/or *CYP2C19*3* in exon 4: homozygous extensive metabolizers, **1/*1*; heterozygous extensive metabolizers, **1/*2* and **1/*3*.

2.4. 24-h intragastric pH monitoring

Before each recording session, a glass electrode (CM-181, Chemical Instruments, Tokyo, Japan) was calibrated in buffer solutions at pH 6.86 and 4.01. At 16:00 h, the pH electrode was inserted through the nose and the tip was fluoroscopically positioned in the upper portion of the gastric corpus (10 cm below the gastroesophageal junction) and connected to a portable digital recorder (CR-5501 or PH-101Z, Chemical Instruments, Tokyo, Japan). At 17:00 h, measurement of intragastric pH was started and continued for 24-h. At fixed times (dinner at 18:00 h, breakfast at 08:00 h, and lunch at 12:00 h), standardized meals were taken (total calories = 1900 kcal/day: protein 70 g, lipids 50 g, carbohydrate 290 g). Subjects were free to drink water during the 24-h period, but were not allowed to smoke though other normal daily activities were not restricted.

2.5. Study protocol

This was a prospective, randomized, open-label, five-way, crossover study. 10 mg tablets of original omeprazole, Omeprazon (Mitsubishi Pharma, Osaka, Japan,

collaboration with AstraZeneca, London, UK, Lot No. L071), and three brands of generic omeprazole, Omeprazole-Towa (Towa Pharmaceuticals, Osaka, Japan, Lot No. C306), Ovulanze (Taiyo Yakuhin, Aichi, Japan, Lot No. 325901) and Omerap (Nichi-iko Pharmaceuticals, Toyama, Japan, Lot No. EP2401) were purchased on the market in December 2004. Results of previous bioavailability/bioequivalence studies between original and generic omeprazole are shown in Table 1 [17-19]. Then, in a randomized order, each subject was repeatedly administered once daily after breakfast either of the four drugs or placebo for 7 consecutive days. Intragastric pH was measured for 24-h five times; on day 7 of each period of repeated administration of the four drugs or placebo. Between each period of administration there was a wash-out period of 2 weeks or more.

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guideline on Human Genome and Genetic Analyses in Japan, and approved by the Ethical Committee of Hiroshima University Hospital. Written informed consent was obtained from all subjects prior to study entry.

2.6. Data analysis

After the 24-h monitoring of intragastric pH, the recorded values were transferred to a personal computer for processing and analysis using a commercially available software program (Chemical Instruments, Tokyo, Japan). The median value of intragastric pH and the percentage of time that intragastric pH was above 4 were calculated. These parameters are widely used and represent the degree of gastric acid suppression.

Nocturnal gastric acid breakthrough (NAB) was defined as at least 60 continuous

minutes of intragastric pH below 4 during the midnight-time period (22:00-06:00 h) [22].

2.7. Statistical analysis

The parameters were expressed as median values with ranges. Differences in median value of intragastric pH and the percentage of time that intragastric pH was above 4 between placebo and each omeprazole formulation were determined by the Wilcoxon signed-rank test. Differences in inter-subject variations of these parameters between original omeprazole and generic omeprazole were compared by the F-test. A *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Intragastric pH profiles

The 24-h intragastric pH (median pH per hour) profiles without medication (placebo) and on day 7 of repeated administration of 10 mg once daily original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap, are shown in Fig. 1. Median values of intragastric pH increased above 4 for 2-h or more after dinner and lunch during administration of both original omeprazole and the three brands of generic omeprazole, compared with the placebo-controlled data. At night time, intragastric pH values continuously increased to approximately 4 with Omeprazon and Ovulanze, however, they only reached about 3 with Omeprazole-Towa and Omerap.

3.2. Median values of intragastric pH

Box-whisker plots of the median values of 24-h intragastric pH without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg Omeprazon, Omeprazole-Towa, Ovulanze or Omerap are shown in Fig 2. Compared with the placebo-controlled data [1.7 (1.6–2.4)], the median values of 24-h intragastric pH increased significantly with both original and generic omeprazole; Omeprazon [2.4 (2.1–3.3), $P < 0.05$], Omeprazole-Towa [2.5 (1.7–4.3), $P < 0.05$], Ovulanze [2.7 (1.7–4.7), $P < 0.05$] and Omerap [2.5 (2.3–3.2), $P < 0.05$].

Compared with Omeprazon, significantly larger range of inter-subject variation was observed in median values of 24-h intragastric pH with Omeprazole-Towa and Ovulanze ($P < 0.05$).

3.3. Percentages of time that intragastric pH was above 4

Box-whisker plots of the percentages of time that intragastric pH was above 4 without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg Omeprazon, Omeprazole-Towa, Ovulanze or Omerap are shown in Fig. 3A and B. Compared with the placebo-controlled data [5% (3–14%)], the percentages of time that intragastric pH was above 4 during 24-h increased significantly with original and generic omeprazole [26% (11–41%) with Omeprazon ($P < 0.05$), 16% (5–58%) with Omeprazole-Towa ($P < 0.05$), 29% (11–54%) with Ovulanze ($P < 0.05$), and 23% (12–43%) with Omerap ($P < 0.05$), respectively]. Compared with Omeprazon, significantly larger range of inter-subject variation was observed in this parameter during 24-h with Omeprazole-Towa ($P < 0.01$) and Ovulanze ($P < 0.05$). On the other hand, during the night-time period (20:00-08:00 h), this parameter also increased significantly with Omeprazon [16% (7–41%) ($P < 0.05$)] and Ovulanze [28% (4–52%)

($P < 0.05$)], compared with the placebo-controlled data [3% (0–18%)], whereas this parameter did not increase significantly with Omeprazole-Towa [8% (0–43%) and Omerap [12% (3–29%)].

3.4. Nocturnal gastric acid breakthrough (NAB)

All subjects experienced NAB on day 7 of repeated administration once daily after breakfast of 10 mg Omeprazon, Omeprazole-Towa, Ovulanze or Omerap. However, compared with the placebo-controlled data, the duration of NAB was significantly reduced during either of original or generic omeprazole ($P < 0.05$) (Table 2).

4. Discussion

This study revealed that the acid-suppressive effects of some brands of generic omeprazole were insufficient, moreover, significantly larger range of inter-subject variation in the effect was observed with some generic omeprazole formulations.

In this study, omeprazole was administered at a low dose, i.e. 10 mg once daily after breakfast, in *H. pylori*-negative CYP2C19 extensive metabolizers, because most GERD patients, who need long-term maintenance therapy with omeprazole, are without *H. pylori* infection [23, 24]. Furthermore, the inter-subject variation of the acid-suppressive effect is smaller in subjects without *H. pylori* infection than in those with such infection [25, 26], and in CYP2C19 extensive metabolizers the acid-suppressive effect of omeprazole 10 mg once daily is not as potent as 20 mg [14]. Therefore, we considered that differences in the acid-suppressive effect would be more clearly revealed among the original and generic omeprazole. In addition, in Japan omeprazole 40 mg is not approved for use as initial therapy for acid-related diseases, only 20 mg or less is

permitted. Furthermore, 10 mg is the dose of omeprazole most often used for maintenance therapy for GERD in Japan.

In Japan, omeprazole is usually administered after breakfast, whereas in many other countries it is administered before breakfast. The bioavailability of omeprazole is thought to be influenced by concomitant food intake. However, no significant difference was observed in the acid-suppressive effect of single oral administration of omeprazole 20 mg between before breakfast and after breakfast [27], as well as in the area under the concentration-time curve (AUC) of omeprazole after single oral administration of omeprazole 20 mg between before breakfast and after breakfast [28, 29]. From this background, we consider that the results of this study are not different from that if omeprazole had been administered before breakfast.

An original product is the first to appear on the market and is patent-protected. In Japan, patents give exclusive production rights for 20–25 years following application. However, with patent expiry other manufacturers can produce and market generic versions of original drugs, which contain the same active ingredients, and this involves verification of the stability, quality and effect (i.e., bioequivalence) of the new product [30]. In general, however, no studies have been required for generic products when they are compared on clinical grounds, e.g., therapeutic or adverse effects, with their original products.

According to previous reports and information provided by each drug manufacturer, there are no significant differences in pharmacokinetic parameters after single oral administration of 10 mg original omeprazole or the three brands of generic omeprazole (Table 1). The effective ingredient of any generic omeprazole is exactly the same as original omeprazole, therefore, it is likely that the reduced acid-suppression and larger

range of inter-subject variation of generic omeprazole results from greater inter-subject variation in the process of intestinal absorption, rather than variation in systemic clearance.

Omeprazole has low water solubility and is degraded by gastric acid, therefore, an acid-resistant formulation of omeprazole, consisting of enteric-coated granules, has been developed for oral use to minimize degradation in the stomach. Previously, stability of each omeprazole formulation, i.e., its dissolution and release, has been tested [31–36], and in some cases bioequivalence could not be proven [31, 35, 36]. Concerning the results of our study, different performance of the granule coating between original and generic omeprazole may be a major determinant of reduced acid-suppression and greater inter-subject variation.

The end-point of this comparative study should be the therapeutic outcomes; because significantly larger range of inter-subject variation of the acid-suppressive effects of generic omeprazole does not necessarily imply therapeutic inequivalence. No significant difference was observed between original and generic omeprazole available in Israel, Omepradex, as part of PPI-based triple therapy for eradication of *H. pylori* [37], although C_{max} and AUC differed significantly between these two formulations after repeated administration [35]. Further clinical comparisons are needed.

5. Conclusion

This prospective study has demonstrated that the acid-suppressive effects of repeated administration of 10 mg once daily after breakfast of three brands of generic omeprazole, Omeprazole-Towa, Ovulanze and Omerap, were not the same as that of original omeprazole, Omeprazon: During the night-time period, the percentages of time

that intragastric pH was above 4 were not significantly higher with Omeprazole-Towa and Omerap than the placebo-controlled data. Moreover, with Omeprazole-Towa and Ovulanze, there were significantly larger range of inter-subject variations in the median values of intragastric pH and the percentages of time that intragastric pH was above 4 for 24-h, compared with Omeprazon.

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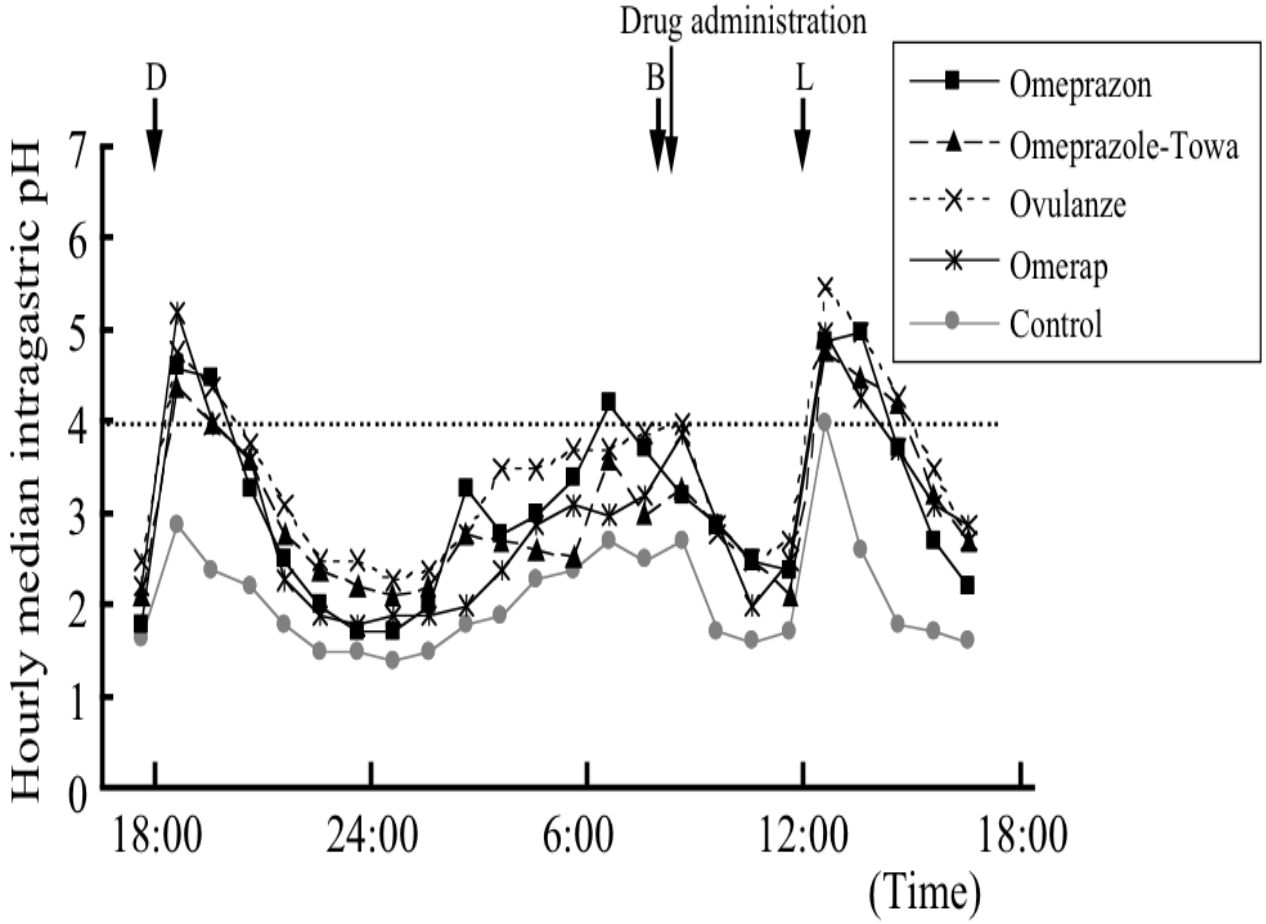
Figure legends

Fig 1. 24-h intragastric pH (median pH per hour) profiles without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap in *H. pylori*-negative CYP2C19 extensive metabolizers. (D, dinner; B, breakfast; L, lunch.)

Fig 2. Box-whisker plots of the median values of 24-h intragastric pH without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap in *H. pylori*-negative CYP2C19 extensive metabolizers. (*$P < 0.05$ vs. placebo-controlled data by the Wilcoxon signed-rank test; #$P < 0.05$ between original omeprazole and generic omeprazole by the F-test.)

Fig 3. Box-whisker plots of the percentages of time that intragastric pH was above 4 during the 24-h (A) and night-time period (20:00-08:00 h) (B) without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap in *H. pylori*-negative CYP2C19 extensive metabolizers. (*$P < 0.05$ vs. placebo-controlled data by the Wilcoxon signed-rank test; #$P < 0.05$ and ##$P < 0.01$ between original omeprazole and generic omeprazole by the F-test.)

Fig. 1


Drug administration
D
B
L
Omeprazon
Omeprazole-Towa
Ovulanze
Omerap
Control
Hourly median intragastric pH
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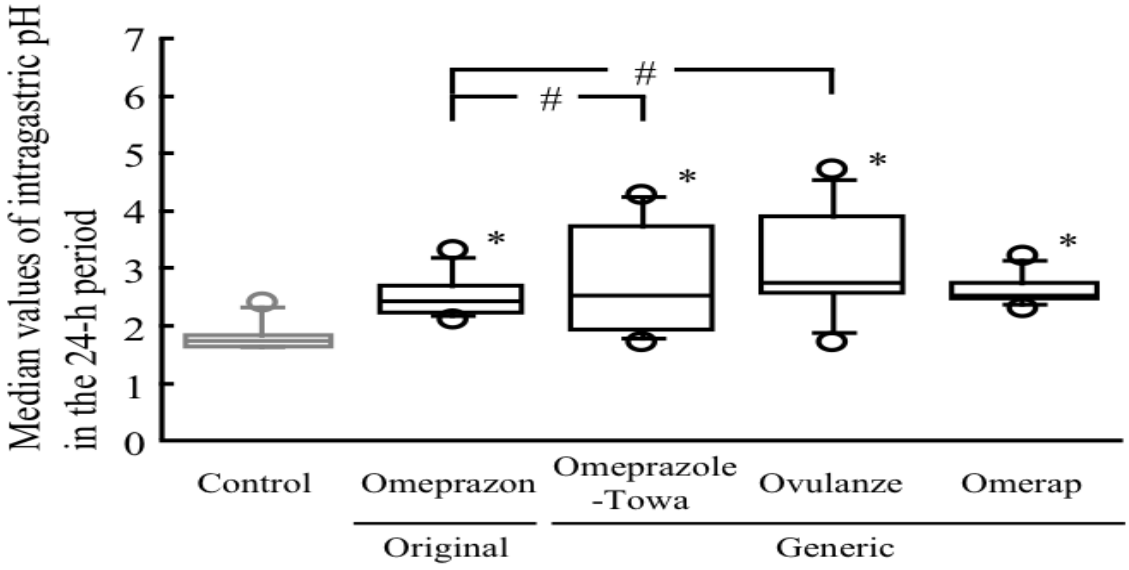
1
2
3
4
5
6
7
18:00
24:00
6:00
12:00
18:00
(Time)

Fig. 2


Median values of intragastric pH in the 24-h period
7
6
5
4
3
2
1
0
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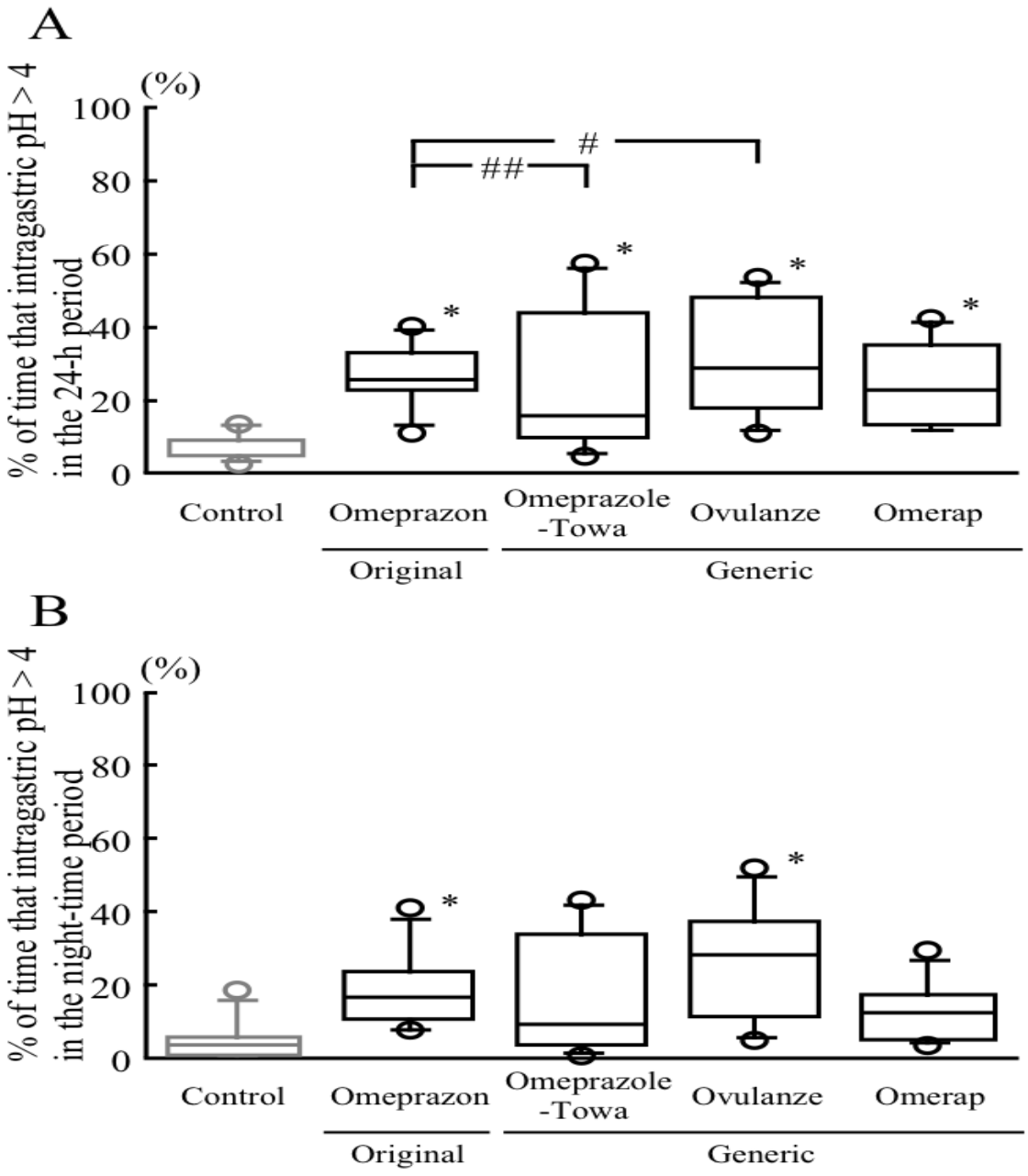
Control
Omeprazon
Omeprazole -Towa
Ovulanze
Omerap
Original
Generic

Fig.3


A
% of time that intragastric pH > 4 in the 24-h period
(%)
100
80
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Control
Omeprazon
Omeprazole -Towa
Ovulanze
Omerap
Original
Generic
B
% of time that intragastric pH > 4 in the night-time period
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Control
Omeprazon
Omeprazole -Towa
Ovulanze
Omerap
Original
Generic

Table 1. Results of bioavailability/bioequivalence studies of single oral administration of 10 mg tablet of original omeprazole and three brands of generic omeprazole, Omeprazole-Towa, Ovulanze and Omerap [17-19].

	Subject no.	C_{max} (ng/ml)	t_{max} (h)	AUC (ng·h/ml)	$t_{1/2}$ (h)	Ref. no.
Omepral*	22**	179.78 ± 107.81	1.95 ± 0.77	199.61 ± 113.13	0.6251 ± 0.2470	
Omeprazole-Towa	22**	183.70 ± 135.43	1.52 ± 0.76	206.40 ± 129.16	0.7864 ± 0.4893	17
Omeprazon	29	279.0 ± 182.6	1.8 ± 0.8	559.1 ± 623.9	1.57 ± 1.58	
Ovulanze	29	266.9 ± 169.6	1.8 ± 1.0	537.6 ± 584.5	1.25 ± 0.68	18
Omepral*,***	20	471.3 ± 314.1	1.85 ± 0.86	1165.5 ± 1452.1	1.40 ± 1.13	
Omerap***	20	429.2 ± 289.0	1.88 ± 0.93	1091.8 ± 1318.5	1.48 ± 0.80	19

Results were expressed as means ± S.D. *Omepral, another original omeprazole available in Japan, AstraZeneca, Osaka, Japan. **Cross-over comparative study in CYP2C19 homozygous extensive metabolizers. ***Cross-over comparative study between 20 mg (two 10 mg tablets) Omepral and 20 mg (two 10 mg tablets) Omerap.

Table 2. Incidence and duration of nocturnal gastric acid breakthrough (NAB) without medication (placebo) and on day 7 of repeated administration once daily after breakfast of 10 mg original omeprazole, Omeprazon, or three brands of generic omeprazole, Omeprazole-Towa, Ovulanze or Omerap, in *Helicobacter pylori*-negative CYP2C19 extensive metabolizers.

	Control	Omeprazon	Omeprazole-Towa	Ovulanze	Omerap
NAB					
Incidence	7/7 (100%)	7/7 (100%)	7/7 (100%)	7/7 (100%)	7/7 (100%)
Duration	480min (285-480min)	242min (238-350min)*	254min (181-480min)*	283min (73-387min)*	308min (172-480min)*

Parameters were expressed as median values with ranges. *$P < 0.05$ vs. placebo-controlled data by the Wilcoxon signed-rank test. Incidence, incidence of NAB; Duration, duration of NAB.