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Alimentary Tract

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

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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, randomised, 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 metaboliser.

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 gastro-oesophageal 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 metabolisers with higher enzymatic activity, heterozygous extensive metabolisers with moderate enzymatic activity and poor metabolisers 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 in 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

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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 in the market in Japan. Studies to determine the bioequivalence between original and generic omeprazoles 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 metabolisers 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 metabolisers (five homozygous extensive metabolisers and two heterozygous extensive metabolisers) 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 centre 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 metabolisers, **1/*1*; heterozygous extensive metabolisers, **1/*2* and **1/*3*.

2.4. Twenty-four-hour 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 gastro-oesophageal 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), standardised meals were taken (total calories = 1900 kcal/day: protein 70 g, lipids 50 g and 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, randomised, open-label, five-way, crossover study. Ten-milligram 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 from the market in December 2004. Results of previous bioavailability/bioequivalence studies between original and generic omeprazoles are shown in Table 1 [17–19]. Then, in a randomised order, each subject was repeatedly administered once daily after breakfast either of the four drugs or placebo for seven consecutive days. Intragastric pH was measured for 24 h five times and 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