



## **Intragastric acidity during administration of generic omeprazole and esomeprazole - a randomized, two-way crossover study including CYP2C19 genotyping**

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**Intragastric acidity during administration of generic omeprazole and esomeprazole - a randomized, two-way crossover study including CYP2C19 genotyping**

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**Intragastric acidity during administration of generic omeprazole and esomeprazole - a randomized, two-way crossover study including CYP2C19 genotyping**

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## **ABSTRACT**

**Objectives:** Generic omeprazole has been approved in many countries for the treatment of acid-related gastrointestinal disorders. However, clinical studies comparing generic to original proton pump inhibitors are limited.

**Methods:** In this randomized, single-blinded, two-way crossover study, 24 healthy H. pylori-negative subjects, received generic omeprazole (Omepr®) 20 mg once daily or esomeprazole 20 mg once daily for five consecutive days. 24-hour intragastric pH was recorded on day 5 of each treatment. CYP2C19 status was determined by polymerase chain reaction-restriction fragment length polymorphism.

**Results:** Over all, there were no statistically significant differences between generic omeprazole and esomeprazole with respect to median intragastric pH (3.5 and 3.9,  $p=0.07$ ), the total hours with intragastric pH > 4 (10.4 and 11.3,  $p=0.29$ ), and during upright (9.6 and 9.1,  $p=0.77$ ) or supine (2.2 and 2.2,  $p=0.94$ ) position. However, in CYP2C19 rapid metabolizers, esomeprazole was superior to omeprazole, with the percentage of time with intragastric pH >3.0 and pH >3.5 being higher with esomeprazole than with generic omeprazole ( $\Delta$  8.7% ( $p=0.026$ ) and  $\Delta$  7.5% ( $p=0.046$ ), respectively).

**Conclusion:** Overall, generic omeprazole 20 mg appears to provide a similar intragastric acid control as esomeprazole 20 mg. However, esomeprazole might be advantageous in subjects with a rapid CYP2C19 metabolizer status.

INTRODUCTION

Proton pump inhibitors (PPI) are the treatment of choice in gastroesophageal reflux disease (GERD) and other acid-related conditions of the upper gastrointestinal tract (1,2). Depending on the clinical indication, approved PPI are usually prescribed in their full or half standard dosages.

Several intragastric pH studies have shown that esomeprazole at a dose of 40 mg daily is superior to standard dosages of all other available original brand PPI's in controlling intragastric acidity (3-7), while high-dose esomeprazole was superior to high-dose pantoprazole in another study (8). This functional superiority of esomeprazole is mirrored by significant clinical advantages over some other PPI's in healing and maintenance therapy of erosive GERD (9,13-15) while there were no differences from omeprazole in the treatment of non-erosive GERD (16).

Generic omeprazole has been approved and is being increasingly used for the treatment of GERD and other acid related gastrointestinal disorders. However, clinical or intragastric pH studies comparing generic omeprazole with other original PPI are sparse. A randomized study in Japanese healthy subjects demonstrated significant differences in intragastric acid control between one original and two generic omeprazole brands (17). Finally, a comparative study of 25 non-Astra authorised omeprazole products suggests significant pharmaceutical differences between various products after storage under forced conditions (18).

Due to differences in the enzymatic hepatic metabolism, the racemic omeprazole and the s-isomer esomeprazole differ in their pharmacokinetic and pharmacodynamic profile (19,20). Esomeprazole is less metabolized by the polymorphic cytochrome P450 2C19 (CYP2C19) than omeprazole. Several studies have shown that genetic polymorphism of CYP2C19 which encodes for different

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3 metabolizer phenotypes (rapid, intermediate and poor metabolizer), affects  
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5 intragastric acid control by PPI's, while different PPI's may be affected differently (21-  
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7 23). Accordingly, the rapid CYP2C19 metabolizer status has been recognized as a  
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9 significant risk factor for treatment failure in GERD and in *Helicobacter pylori*  
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11 eradication therapy (24).  
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15 The aim of this study was to compare the effect of generic omeprazole 20 mg  
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17 per day with esomeprazole 20 mg per day on intragastric acidity, and to investigate  
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19 the influence of the CYP2C19 metabolizer status.  
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## MATERIALS & METHODS

### *Subjects*

Healthy men and women between 18 and 60 years of age were recruited by local advertisement at the University Hospital Dresden. The subjects were considered healthy based on a detailed medical history, physical examination and routine laboratory assessment. Only subjects who were *H. pylori* negative based on  $^{13}\text{C}$  urea breath test (INFAI, Cologne, Germany) were eligible. Subjects with past or present significant illness and those with known intolerance to PPI were excluded. Women with childbearing potential were required to use accepted birth control methods. Further exclusion criteria were pregnancy, lactation, abnormal laboratory values at baseline, and drug or alcohol abuse. Antisecretory drugs including PPI, H<sub>2</sub> receptor antagonists, prokinetic drugs or any other agents that could affect the pharmacokinetics or absorption of PPIs were not allowed during the study or within two weeks before randomisation. All subjects gave written informed consent prior to enrolment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the local institutional review board at the University Hospital in Dresden.

### *Study design and procedures*

In this randomized, investigator-blinded, two-way cross-over study each subject received either generic omeprazole (Omepr®, Hexal AG, Holzkirchen, Germany) 20 mg once daily or esomeprazole (Nexium mups®, AstraZeneca, Wedel, Germany) 20 mg once daily for five consecutive days according to a computer-generated randomization list. Crossover administration of the study drug followed after a washout period of 14 days (+/- 3 days). The study drug was placed into identically

looking white screw-cap plastic container. Each tablet was swallowed unchewed by the study subject between 7.30 and 8 AM together with 200 ml of water 30 minutes before meal for five consecutive days under direct supervision of the study physician, thereby providing 100% compliance. Subjects were instructed to avoid smoking and alcohol consumption during the entire treatment period and to lie down only at night-time hours between 10 PM and 6 AM. They were also encouraged to report adverse events spontaneously. Tolerability of the study drug was assessed each day during the treatment period.

#### *Assessment of intragastric pH*

An ambulatory continuous 24-h intragastric pH recording was performed on day 5 of each dosing period. The 24-h intragastric pH was recorded using a microelectrode (Ion sensitive field effect transistor, Veraflex®, Alpine Biomed Corp.) with an internal reference electrode linked to a Digitrapper 100® (Medtronic GmbH, Düsseldorf). The calibrated microelectrode was positioned 10 cm below the manometrically located lower oesophageal sphincter at 7.30 AM prior to breakfast and the administration of the study drug, and was removed the following morning at 8 AM. The electrode was calibrated before and after each recording. Intragastric pH was evaluated every 4 s and recorded on the attached Digitrapper. All pH measurements were assessed by a single gastroenterologist who was blinded to the study group.

#### *CYP2C19 genotyping*

Cytochrome P450 2C19 (CYP2C19) genotypes were determined by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). Genomic DNA was extracted from whole blood and was PCR-amplified using published allele-



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specific primers. PCR products were digested using the restriction endonucleases SmaI and BamHI, and visualized by 3% agarose gel electrophoresis. Based on the PCR-RFLP result, subjects were classified as rapid metabolizer (RM), intermediate metabolizer (IM) or poor metabolizer (PM). Appropriate controls were included in each PCR analysis set.

Statistics

The sample size calculation was based on the data published by Lind et al. (3). The primary endpoint of the study was the time spent with an intragastric pH >4 within 24 h. We hypothesized that for generic omeprazole the time with intragastric pH >4 would be ≥10% lower compared to original omeprazole. For esomeprazole, 12.3 to 12.7 h spent with an intragastric pH >4 was assumed (3). Based on these assumptions, a sample size of 24 subjects was considered sufficient to show a statistically significant difference in favour of esomeprazole.

We analyzed data from a two-dosing, two-period (2 x 2) cross-over design using a random effects model modelling the carryover effect from one period to the next, the treatment (drug) effect and the period effect. First the assumptions of using a crossover design were tested. The results showed that there was neither a carryover effect from one period to the next nor a period effect for all of the investigated measures. P values <0.05 were considered significant. Results are given as averaged means and their differences, including the 95% confidence interval.

## RESULTS

### *Subject characteristics*

Thirty-two healthy Caucasian subjects were screened. Eight subjects were excluded due to lack of adequate availability (n=4), pregnancy (n=1) or technical problems (n=3). Twenty-four subjects were randomized and available for complete analysis (13 females, mean age 24.7 years, mean body mass index 22.1 kg/m<sup>2</sup>).

### *Intragastric pH*

The mean number of hours with available pH recordings on day 5 was 23.89 h (23.3-24.0) with generic omeprazole and 23.84 h (22.6-24.0) with esomeprazole. There were no statistically significant differences in intragastric pH values on day 5 between generic omeprazole 20 mg per day and esomeprazole 20 mg per day (Table 1). Overall, there were no significant differences between generic omeprazole and esomeprazole with respect to different intragastric pH thresholds (Figure 1).

### *CYP2C19 status*

By CYP2C19 genotyping, 16 subjects were classified as having an **RM** status and 8 as having an IM status. There were no subjects with a PM status. With respect to the median intragastric pH and the time spent with an intragastric pH >4 time, there were no significant differences between generic omeprazole and esomeprazole subjects with an **RM** and IM status, respectively (Table 2). However, the percentage of time with intragastric pH >3.0 and pH >3.5 was significantly higher with esomeprazole compared to generic omeprazole in subjects with an **RM** status ( $\Delta$  7.5% (p=0.046) and  $\Delta$  8.7% (p=0.026), respectively). Otherwise, there were no significant differences

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between the two study drugs with respect to other intragastric pH thresholds (Figure 2).

*Side effects*

In total, only 4 subjects reported mild adverse events. There were no serious adverse events. With generic omeprazole, diarrhea, flatulence and bloating was reported once each. With esomeprazole, headache was reported twice, and nausea once.

## DISCUSSION

To our knowledge, this is the first study to compare equivalent dosages of generic omeprazole and esomeprazole in healthy Caucasian subjects. In our view, the results of the study are clinically relevant, since generic omeprazole brands are increasingly used for the treatment of acid related upper gastrointestinal disorders, while clinical data to support this strategy are clearly limited and controversial.

In our study population, the level of intragastric acid suppression with esomeprazole 20 mg daily was comparable to that reported by Lind et al. (3). Moreover, the level of intragastric acid suppression obtained with generic omeprazole 20 mg daily was also in the range of data reported by other pH studies using original brand omeprazole (3,5,7). Given the validity of the comparator in our study (esomeprazole), it appears that the generic omeprazole used in our study provides a similar degree of intragastric acid suppression.

Esomeprazole 20 mg daily has been proven effective for maintenance therapy of erosive GERD (14,15), for on-demand therapy in non-erosive GERD (25,26) and for prevention of gastroduodenal ulcers in patients with non-steroidal antiinflammatory drugs (27). Since other intragastric pH studies and pharmaceutical studies have suggested significant differences between different generic omeprazole products (17,18), the question remains whether generic omeprazole can provide a similar clinical efficacy as other original PPI brands. Although the results of our intragastric pH study can not be directly transferred to clinical outcomes, we speculate, that the generic omeprazole used in our study with a daily dose of 20 mg **might** offer a similar clinical benefit in the treatment of acid-related gastroduodenal disorders as **other original brand PPIs**. Ideally, this hypothesis should be tested by adequately sized randomized clinical trials which are, of course, unlikely to be conducted. However,

two randomized controlled trials have shown that omeprazole 20 mg daily was comparable to esomeprazole 20 mg daily in the treatment of non-erosive and erosive gastroesophageal reflux disease (16,28).

The CYP2C19 metabolizer status has been shown to affect intragastric acid suppression by PPI's, as well as the clinical efficacy of PPI's in the treatment of GERD and in *Helicobacter pylori* eradication therapy (24). In particular, the rapid metabolizer status has been identified as significant risk factor for treatment failure in Asian patient populations. In our study, which was not powered to detect differences between the two drugs in subgroups, we found nevertheless a better acid control with esomeprazole compared to generic omeprazole in subjects with an rapid metabolizer status, the time spent with an intragastric pH above 3.0 and 3.5, respectively, being significantly longer with esomeprazole than with generic omeprazole. The pH threshold of 3 is of clinical relevance with respect to healing of duodenal ulcers (29). Whether this finding is also clinically relevant in patients with GERD remains unclear, since an intragastric pH threshold of 4 appears to be critical for the effectiveness of PPI in the treatment of erosive GERD (30). This finding does not come as a surprise, since the S-isomer esomeprazole is metabolized to a greater extent via the cytochrome 3A4 subunit than the racemic omeprazole (19,20). Accordingly, data from randomized clinical studies in Caucasian GERD patients at least suggest that the efficacy of esomeprazole is not affected by the CYP2C19 metabolizer status (31).

In addition, the proportion of individuals with a rapid, intermediate or poor CYP2C19 metabolizer may vary between different ethnic populations, and different PPI's may be affected differently (24). For example, in Asian populations the frequency of poor metabolizer is around 22% while in among Caucasians only about 3% harbor a poor metabolizer status (32,33). Therefore, the determination of the

CYP2C19 metabolizer status may only be of limited value for clinical practice in Caucasian patients.

In summary, our study suggests that generic omeprazole 20 mg once daily provides a similar intragastric acid control as esomeprazole 20 mg once daily in healthy volunteers. However, esomeprazole provides better acid control in the subgroup of CYP2C19 rapid metabolizers. Further studies are needed to evaluate whether this advantage translates into clinical effectiveness.

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TABLES

Table 1: Intragastric pH on day 5 of generic omeprazole and esomeprazole in 24 healthy subjects

	Generic omeprazole 20 mg per day	Esomeprazole 20 mg per day	P
Hours with pH > 4 (range)	10.4 (3.0 – 20.2)	11.3 (3.7 – 18.0)	0.29
% of time with pH > 4 (range)	43.5 (12.4 – 83.9)	47.5 (15.5 – 75.3)	
% of time with pH > 4 - upright (range)	52.7 (17.7 – 96.9)	59.9 (24.2 – 88.0)	0.18
- supine (range)	24.8 (0.0 – 60.1)	25.7 (1.2 – 58.7)	0.81
Median pH (range)	3.5 (1.6 – 5.3)	3.9 (1.9 – 5.1)	0.07
Subjects with pH > 4 for at least 12 h (%)	9 (37.5)	11 (45.8)	0.75

Table 2: Intragastric pH on day 5 with generic omeprazole and esomeprazole in rapid metabolizers (RM) and intermediate metabolizers (IM)

	Generic omeprazole 20 mg per day	Esomeprazole 20 mg per day	P
Hours with pH > 4 (range)			
% of time with pH > 4 (range)			
- RM	9.4 (3.0 – 16.1)	11.1 (3.7 – 18.0)	0.29
- IM	39.2 (12.4 – 67.3)	46.5 (15.5 – 75.3)	
	12.1 (6.7 – 20.2)	12.2 (4.8 – 15.7)	0.18
	50.4 (28.0 – 83.9)	51.1 (19.8 – 65.8)	
Median pH (range)			
- RM	3.3 (1.6 – 5.1)	3.8 (1.9 – 5.0)	0.08
- IM	3.8 (2.0 – 5.3)	4.1 (2.7 – 5.1)	0.42
Subjects with pH > 4 for at least 12 h (%)			
- RM	5 (31.2)	7 (43.8)	0.69
- IM	4 (50.0)	4 (50.0)	1.0

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**LEGENDS**

Figure 1: Mean percentage of time above intragastric pH tresholds in rapid (RM) and intermediate metabolizers (IM)

Figure 2: Individual percentage of time above intragastric pH tresholds in rapid (RM) and intermediate metabolizers (IM)

For Peer Review

Figure 1

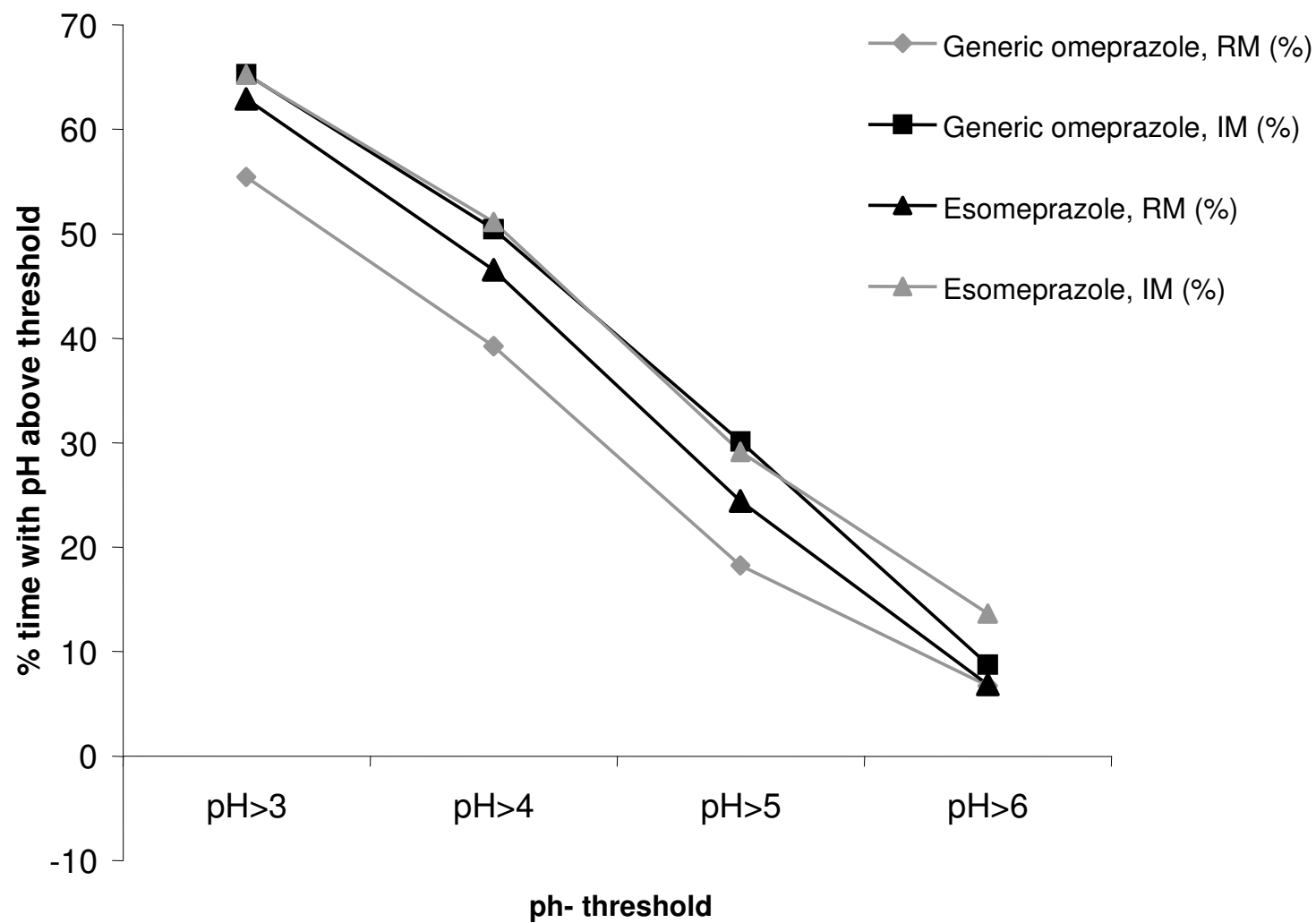




Figure 2

