Antimicrobial activity of esomeprazole versus omeprazole against Helicobacter pylori

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Received 20 June 2002; returned 8 August 2002; revised 9 September 2002; accepted 11 November 2002

Objective: Esomeprazole is an enantiomorph of omeprazole, which inhibits gastric acid secretion more effectively than omeprazole. As proton pump inhibitors also exert an antibacterial activity, we aimed to compare esomeprazole and omeprazole for their antimicrobial activity against Helicobacter pylori in vitro.

Methods: We studied 52 H. pylori isolates obtained from gastric biopsies and inoculated onto agar plates containing the acid-converted drugs at different concentrations. The minimal concentrations that inhibited the growth of 50% and 90% of isolates were defined as MIC₅₀ and MIC₉₀.

Results: The MIC₅₀ and MIC₉₀ of esomeprazole were 16 and 32 mg/L; and those of omeprazole were 32 and 64 mg/L. Overall, 63.5% of isolates showed the same susceptibility to both drugs; 17 isolates were two- to 64-fold more susceptible to esomeprazole and two isolates were two-fold more susceptible to omeprazole.

Conclusions: The increased antimicrobial activity in vitro of esomeprazole against H. pylori could contribute to improving the outcome of the eradication treatment of such an infection.

Keywords: Helicobacter pylori, omeprazole, esomeprazole, antimicrobial activity

Introduction

Benzimidazole compounds, such as omeprazole and lansoprazole, are gastric parietal cell proton pump inhibitors (PPIs), which are widely used for the treatment of acid-related gastric diseases due to their ability to inhibit acid secretion.¹ After oral administration, they are converted into a sulfenamide derivative by gastric acid (proton-dependent activation) and inhibit the acid pump, the H⁺/K⁺-ATPase of the gastric parietal cells. Based on the evidence that a less acidic environment may enhance antibiotic activity in the gastric milieu, they are also given in association with antimicrobial agents for the eradication of Helicobacter pylori infection. The current European guidelines for the treatment of H. pylori infection indicate a PPI-based triple therapy (usually a PPI together with two antibiotics chosen from amoxicillin, clarithromycin and metronidazole) as the first choice treatment.² Besides their inhibitory effect on acid secretion, PPIs have also been shown to exert an antibacterial activity in vitro, which is selective to H. pylori.³ Such antimicrobial power is common to all benzimidazoles and absent in other antisecretory drugs such as H₂-antagonists.⁴,⁵ However, the mechanism by which these compounds exert their antibacterial effect is still an open question.⁶ Esomeprazole is a new PPI and is the first PPI that has been developed as an optical isomer (L-isomer). It is optically stable in humans with negligible inversion to the R-isomer. Its oral bioavailability is higher than omeprazole, resulting in greater acid suppression.⁷ The aim of this study was to compare the antimicrobial activity of omeprazole and esomeprazole against a panel of H. pylori isolates.

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Materials and methods

Isolates and growth conditions

Strains of *H. pylori* used for omeprazole and esomeprazole susceptibility tests included 52 isolates from adult patients complaining of upper gastrointestinal symptoms at S. Orsola Hospital, Department of Internal Medicine and Gastroenterology, Bologna, Italy. Informed written consent was obtained from all patients. The endoscopies were performed by the same investigator (D.V.), using an Olympus GIF 100 videendoscope. During the test, biopsies were taken for histology, urease test and culture. Patients who were taking PPIs, H2 receptor antagonists, non-steroidal anti-inflammatory drugs or antibiotics in the 4 weeks preceding the study were excluded. Gastric mucosa biopsies were cultured on Columbia agar containing 5% horse blood, 10 mg/L vancomycin, 5 mg/L trimethoprim, 20 U/mL polymixin B and 7.5 mg/L nalidixic acid. Plates were incubated in a microaerobic environment obtained by using an anaerobic jar with a gas-generating pack for creating a microaerophilic atmosphere (Oxoid Camp GasPak; Oxoid, Unipath, Garbagnate Milanese, Italy). Plates were incubated at 37°C for 7 days, and inspected daily from the third day. Colonies resembling *H. pylori* were identified by Gram’s stain and by oxidase, catalase and urease tests. Stock cultures were stored at –80°C in Brucella broth with 10% fetal calf serum supplemented with 20% glycerol.

MIC determinations

Plates for the susceptibility test were freshly prepared. MIC50 and MIC90 were determined using an agar dilution method as described by Figura et al. Briefly, both drugs were dissolved in dimethylsulphoxide (DMSO) at 10 mg/mL and diluted 1:4 in citrate buffer pH 3 at 4°C for 120 min. Exposure to low pH transforms the drug into its protonated ‘active’ metabolite, the sulfenamide. The drugs were incorporated in melted agar containing 5% sheep blood, cooled to 60°C, at concentrations ranging from 0.125 to 128 mg/L. A saline suspension of *H. pylori* equivalent to McFarland opacity standard 2 (containing 1 × 107 cfu/mL) was prepared and inoculated (3 µL/spot) onto the agar using a Steer Apparatus. Once inoculated, plates were dried at room temperature under a biological hood, incubated at 37°C in a microaerobic atmosphere (Oxoid Camp GasPak) and read after 2–3 days. The MIC50 and MIC90 were taken as the lowest concentrations of omeprazole and esomeprazole at which the growth of at least 50% and 90%, respectively, of isolates tested was completely inhibited. Each test was performed in triplicate. Means, median and confidence intervals were determined and Wilcoxon matched-pair signed ranks test was performed using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

Results

The characteristics of patients from whom isolates were obtained are shown in Table 1. The minimal concentrations of esomeprazole at which the development of ≥50% and ≥90% of isolates tested was inhibited were 16 and 32 mg/L; those of omeprazole were 32 and 64 mg/L. The mean and median MICs of esomeprazole were 25.07 mg/L (95% CI, 17.99–32.16) and 16 mg/L; those of omeprazole were 29.33 mg/L (95% CI, 23.00–35.67) and 32 mg/L. The difference between the median MICs of esomeprazole and omeprazole differed significantly from zero (*P* = 0.0028). Thirty-three isolates (63.5%) showed the same susceptibility to both PPIs; 17 isolates (32.7%) were two- to 64-fold more susceptible to esomeprazole and two isolates (3.8%) were two-fold more susceptible to omeprazole. Figure 1 shows in detail the MICs for the 19 isolates with different susceptibilities to PPIs.

Discussion

*H. pylori* infection is a *sine qua non* for duodenal ulcer development. The antimicrobial activity of PPIs may reside in their structural similarity to imidazoles (metronidazole and tinidazole) and/or in the anti-urease effect they exert. Whatever the explanation is, recent studies have shown that PPIs differ in their antibacterial activity, the level of which may depend on their pharmacological properties. Esomeprazole is the L-isomer of omeprazole and it is the first PPI that has been synthesized as an optical isomer to become available for clinical use, with negligible inversion to the R-isomer in humans. Its oral bioavailability is higher than that of omeprazole—which results in higher bioavailability and in greater acid suppression—and its pharmacokinetics in the different individuals is more consistent—which leads to an increased delivery of the drug to the gastric parietal cell proton pump and to a superior acid control in vivo. These observations prompted us to compare the MICs of omeprazole and those of its L-isomer for *H. pylori* isolates. Before the execution of the susceptibility test, we acid-converted the drugs, because such an ‘activation’ (with a sulphonamide formation), which
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occurs *in vivo* in the gastric parietal cells, enhances the bactericidal activity of the drug. This phenomenon is irreversible, and once the sulfenamide is produced, the drug can be added to media with different pH values (within the range of optimal growth for this species) without loss of activity. We are not aware of any direct demonstration of the steps leading to the activation of esomeprazole, but, given its similarity to omeprazole, it is very likely to undergo the same process. We found that 63.5% of the isolates showed the same degree of susceptibility to esomeprazole and omeprazole and that 32.7% were two- to 64-fold more susceptible to esomeprazole than to omeprazole. Finally, the MIC$_{90}$ of esomeprazole was lower than that of omeprazole. A two-fold difference in MICs may not be considered significant; however, we believe that every difference may be important, because we do not know the *in vivo* concentrations of PPIs and because in the field of antibiotics, e.g. clarithromycin, a two-fold discrepancy in MICs, for example 2 and 4 mg/L, can make the difference between resistant and susceptible isolates. Are our results clinically relevant? To date only two clinical trials have been published comparing esomeprazole with omeprazole to eradicate *H. pylori* infection. The first one showed that the administration of esomeprazole once a day versus omeprazole twice a day with amoxicillin and clarithromycin was equally effective in eradicating the infection. The second one showed that treatment with esomeprazole was more effective than treatment with omeprazole, even though the difference was not significant (91% of patients were cured with esomeprazole–amoxicillin–clarithromycin versus 88% with omeprazole–amoxicillin–clarithromycin, $P > 0.05$). In conclusion, our study showed that susceptibility of *H. pylori* strains to esomeprazole was globally increased. This antimicrobial activity, in combination with a better control of acid secretion and the once a day administration, makes esomeprazole, associated with two antimicrobial agents, a worthy component of the eradication therapy of *H. pylori* infection.

**References**


