Clinics and Research in Hepatology and Gastroenterology (2017) 41, 575—584

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

ORIGINAL ARTICLE

The effect of omeprazole treatment on the gut microflora and neutrophil function

Maja Kostrzewska[a,*], Agnieszka Świdnicka-Siergiejko[a], Dorota Olszańska[b], Grażyna Jurkowska[a], Marzena Garley[c], Wioletta Ratajczak-Wrona[c], Ewa Jabłońska[c], Jacek Jamiołkowski[d], Andrzej Dabrowski[a]

[a] *Department of gastroenterology and internal medicine, medical university of Bialystok, ul. Sklodowska-Curie 24A, 15-276 Bialystok, Poland*
[b] *Department of microbiological diagnostics and infectious immunology, university hospital of Bialystok, Bialystok, Poland*
[c] *Department of immunology, university hospital of Bialystok, Bialystok, Poland*
[d] *Department of public health, university hospital of Bialystok, Bialystok, Poland*

Available online 1 March 2017

Summary
Background and aim: Proton pump inhibitors (PPIs) may increase the risk of *Clostridium difficile* infections. There are interactions between gut microbiota and innate immune cells including neutrophils. We evaluated the effect of treatment with omeprazole on the gut microflora and neutrophil function.
Methods: In 50 patients, we evaluated the effect of 4-week omeprazole treatment ($n = 25$ with 20 mg per day and $n = 25$ with 20 mg twice daily) on intragastric pH, results of stool culture and lactulose hydrogen breath test (LHBT) and neutrophil function.
Results: The treatment caused significant increase of the mean intragastric pH, especially in the group with 20 mg omeprazole twice daily (from 2.05 ± 0.59 to 5.06 ± 1.6, $P < 0.001$). In LHBT, the increase of hydrogen concentration was observed in higher percentage of patients with 20 mg of omeprazole twice daily, compared to patients with the lower dose (42.1% vs 29.4%; ns). Four weeks of omeprazole treatment have caused considerable changes in stool culture results. Patients treated with higher dose of omeprazole have had some tendency to decrease diversity of colonic microflora in comparison with patients treated with the lower dose of omeprazole. Treatment with omeprazole did not result in *C. difficile* positive stool culture and had no significant effect on neutrophil function.

* Corresponding author.
E-mail address: maja_kost@poczta.onet.pl (M. Kostrzewska).

http://dx.doi.org/10.1016/j.clinre.2017.01.004

Conclusions: Omeprazole treatment have caused considerable changes in stool culture results. Patients treated with the higher dose had some tendency to decreased diversity of colonic microflora and towards changes in fermenting bacteria of the gut. The potential effect of omeprazole on gut microflora does not depend on neutrophil function deterioration.

Introduction

Proton pump inhibitors (PPIs) are currently prescribed on a large scale around the world and they are considered safe and effective drugs. Additionally, many patients are treated with PPIs without approved indications. Therefore, an increasing number of patients is being exposed to side effects of this treatment [1]. The most common of side effects (headache, diarrhea, abdominal pain, nausea, vomiting, flatulence) occur in 5% of patients. Among clinically relevant side effects are: increased risk of bacterial infections [2,3], malabsorption of calcium [4], vitamin B12 [5] and iron (resulting from iatrogenic hipochlorhydria) [6] and the formation of fundic gland polyps in patients on long-term PPI therapy [7]. Some studies also suggest that PPIs can affect the neutrophil functions such as chemotaxis, adhesion to endothelial cells and phagocytosis. The effect of these drugs on neutrophils has been evaluated mostly in vitro, in animal models and in patients with *Helicobacter pylori* infection [8—13].

Since PPIs strongly inhibit the secretion of hydrogen ions by the gastric parietal cells, they are widely used in the treatment of gastroesophageal reflux disease and peptic ulcer disease. However, the inhibition of gastric acid secretion can also trigger pathways leading to unwanted events. Hydrochloric acid provides an important protective barrier of defense against bacterial infections and the increase of intragastric pH may facilitate colonization of the gut by microbiota normally restricted to gastrointestinal tract above the stomach. In some situations, it may predispose to small intestinal bacterial overgrowth (SIBO) or gastrointestinal infections [14]. *Salmonella* is an acid-sensitive bacteria unable to survive in pH < 3. The increased risk of *Salmonella* infection has been reported not only in patients after gastrectomy but also in patients taking PPIs [15]. The drugs inhibiting gastric acid secretion have been also proven risk factor for infection with *Campylobacter* [16,17]. Since the greater risk of gastrointestinal infection has been associated mostly with the PPIs rather than H2-receptor antagonists treatment, it may suggest the correlation between degree of inhibition of gastric acid secretion and the incidence of gastrointestinal infection. On the other hand, although *Escherichia coli* is an acid-sensitive organism, infections with these bacteria have not been reported more common in patients taking PPIs [3,14].

Gastric acid suppression is considered as a risk factor of *Clostridium difficile*—associated diarrhea (CDAD) [14,18]. The risk of *C. difficile* infection (CDI) ranged from 1.4 to 3.5 times higher among patients with PPI treatment compared with those without PPI therapy [19—22]. Several studies reported that PPI administration may lead to changes in human gastrointestinal microbiota and reduce microbial diversity. Furthermore, in the gut microbiome of PPI-users significant changes in the amount of taxa that are associated with increased risk of CDI (*Enterococcaceae* and *Streptococcaceae*) were observed [23—25].

PPIs may also bind and inhibit non-gastric H^+/K^+-ATPases in bacteria and human cells including neutrophils and thereby impair the human immune status [9]. There is an increasing body of evidence about the interactions between gut microbiota and innate immune cells including neutrophils [26,27]. Consequently, PPIs have the potential of gut microbiota modulation by two independent pathways — through inhibition of gastric acid secretion and by the impact on neutrophil function.

Therefore, the aim of this study was to evaluate the effect of 4-week outpatient treatment with oral omeprazole on human gut microbiota and function of neutrophils *in vivo*.

Patients and methods

Before enrolling to the study, all the subjects had clinical examination and laboratory blood tests: complete blood count, concentration of C-reactive protein, fibrinogen, creatinine, urea, bilirubin, glucose, sodium, potassium in serum, activity of alanine aminotransferase and aspartate aminotransferase in serum, prothrombin time and urinalysis. The study has involved patients with normal results of physical examination and laboratory tests before enrollment. Other inclusion criteria were: no PPI treatment at least 14 days before the study, indications for use of PPI (dyspepsia, gastroesophageal reflux disease), no other medications during the study. One patient in omeprazole 20 mg twice daily group was exposed to antibiotics 2 months before enrolling to the study and 9 patients (5 in omeprazole 20 mg once daily group and 4 in omeprazole 20 mg twice daily group) were exposed to PPIs 4—8 weeks before the study. Exclusion criteria were: PPI or H2 receptor antagonist treatment within 14 days before the study, antibiotic use within 4 weeks before the study, current bacterial or viral infection, diabetes, cancer, immunodeficiency in medical history. Informed consent was obtained from all of the subjects. The study was approved by the Ethics committee of medical university of Bialystok.

We have prospectively enrolled 33 women and 17 men. The mean age of the subjects was 42.8 ± 16.1 years. A proton pump inhibitor was randomly selected and administered orally for 4 weeks: 25 patients were treated with omeprazole 20 mg per day (taken 30 minutes before breakfast)