Digestive and Liver Disease 46 (2014) 125–130

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

The effects of long-term therapy with proton pump inhibitors on meal stimulated gastrin

Hólmfridur Helgadóttir[a], David C. Metz[b,*], Yu-Xiao Yang[b], Andrew D. Rhim[b], Einar S. Björnsson[c]

[a] Faculty of Medicine, University of Iceland, Medical Faculty, Reykjavík, Iceland
[b] Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[c] Division of Gastroenterology and Hepatology, Department of the Internal Medicine, The National University Hospital of Iceland, Reykjavík, Iceland

ARTICLE INFO

Article history:
Received 21 June 2013
Accepted 23 September 2013
Available online 6 November 2013

Keywords:
Dyspepsia
Gastrin
GERD
Proton-pump inhibitors

ABSTRACT

Background: Dyspepsia develops in healthy volunteers after withdrawal of proton-pump inhibitors. This phenomenon, attributed to rebound acid hypersecretion, is thought to be mediated by reflex hypergastrinemia.
Aims: To measure fasting and postprandial gastrin in patients on long-term proton-pump inhibitor treatment and correlate gastrin levels with the duration of treatment and other potential predictors.
Methods: In this cross sectional study patients, with erosive esophagitis, on long-term proton-pump inhibitor treatment and healthy controls underwent gastrin measurements at baseline and four times following a meal and *Helicobacter pylori* status was determined.
Results: A total of 100 patients and 50 controls were studied. Pre- and postprandial gastrin levels were higher in patients ($p < 0.001$). No significant correlation was found between the area under the gastrin-curve and the treatment duration. Female patients had significantly higher gastrin levels than males pre- and postprandial, whereas such differences was not found in the control group. Female gender was the only independent predictor of s-gastrin levels (OR 2.50 compared to males, 95% CI: 1.08–5.76, $p = 0.032$) in the patient group.
Conclusion: Gastrin values were higher in patients compared to controls. There was no correlation between gastrin levels and treatment duration. Female patients had significantly higher gastrin values than males.

1. Introduction

Withdrawal of short-term proton-pump inhibitor (PPI) therapy has been shown to induce dyspeptic symptoms in healthy volunteers in comparison to those randomized to placebo [1,2]. This phenomenon, called rebound acid hypersecretion (RAHS), is thought to result from hypergastrinemia as a consequence of inhibition of acid production and its hypertrophic effects on enterochromaffin-like (ECL) cells in the stomach, leading to increased acid production after therapy is discontinued [3,4]. The results of studies assessing RAHS following withdrawal of PPI therapy have been conflicting [1,2,5–7]. Two studies in asymptomatic healthy volunteers found that approximately 44% developed acid-related symptoms following cessation of PPI therapy [1,2]. However, three studies, in patients with gastroesophageal reflux disease (GERD), failed to elicit symptoms after withdrawal of PPIs [8–10].

Longer duration of PPI therapy is associated with a lower likelihood of being able to decrease from twice daily to once daily PPI therapy in GERD patients [5] supporting the contention that long-term therapy may be associated with RAHS. Serum gastrin was also found to be an independent predictor of PPI dependence in a study on discontinuation of PPIs after long-term treatment [6]. However, studies of RAHS in patients after long-term PPI therapy are largely lacking. If RAHS causes exacerbation of symptoms in patients after treatment is discontinued it might lead to a physical "dependence" on acid suppressive therapy, an issue of significant clinical and economic interest.

The primary aims of the current study were to evaluate the effect of long-term PPI therapy on serum gastrin concentrations after a meal and to determine predictors of serum gastrin and chromogranin A (CgA) levels (an indirect measure of ECL cell status [3]) among PPI user and PPI non-users, respectively. These data might

* Corresponding author at: Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, 9 Penn Tower, 1 Convention Avenue, Philadelphia, PA 19104, USA. Tel.: +1 215 662 4279; fax: +1 215 349 5915.
E-mail addresses: hoh19@hi.is (H. Helgadóttir), david.metz@uphs.upenn.edu (D.C. Metz).

1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.09.021

lead to a better understanding of the potential long-term effects of PPIs on the gastric mucosa.

2. Methods

2.1. Study population

We conducted a cross sectional study including 100 patients with endoscopic verified erosive esophagitis (EE) and 50 healthy controls. All patients were identified from endoscopy reports from The National University Hospital of Iceland between 2005 and 2010 with the diagnosis of EE ($n = 1431$). Patients less than 18 years old or greater than 80 years of age were excluded. Other exclusion criteria are listed in the supplementary methods and supplementary Fig. S1. Following the exclusions patients who had received at least 2 years of PPI therapy were identified by comparing the hospital endoscopic database with a nationwide pharmaceutical database of outpatient pharmacy prescriptions run by the Directorate of Health in Iceland. By comparing the two databases as mentioned, we were able to recruit confirmed EE patients with good adherence to therapy. Good adherence was defined as daily and continuous use of PPIs shown by regular prescription renewals in the database. We listed individuals who had at least one prescription over a 4-month period, there were a total of 559 prescriptions in 245 subjects. We excluded individuals who had received PPIs continuously for less than 2 years, those who took PPI on demand and those who had registered address far away from the study center (Appendix A and supplementary Fig. S1). After these exclusions 176 individuals remained and an informal letter was sent to them. Those who could be contacted by phone were then recruited consecutively.

As a control group 50 healthy subjects with no gastrointestinal complaints, that is PPI non-users, were recruited from hospital staff, their friends and relatives and matched for gender and age (±5 years).

2.2. Study design

Study subjects visited the clinic on one occasion after an overnight fast. Two blood samples for fasting serum gastrin and one for serum CgA were obtained before the participants consumed a standardized test meal. The test meal consisted of two slices of whole grain bread with butter and cheese, a boiled egg and a glass of milk (766 kcal in toto). Blood samples for gastrin were also obtained 30, 45, 60 and 90 min after the participants finished their meal. All subjects were tested for the presence of *Helicobacter pylori* infection with a serology test and a ^{14}C urea breath test. On enrollment information was obtained about prior PPI use (dosage and duration) in addition to past medical history, tobacco and alcohol use. The PPI group was divided into three subgroups regarding duration of exposure; 2–5 years, 5–10 years and > 10 years.

2.3. Serum gastrin analysis

Blood was collected in gel tubes, left to coagulate for a minimum of 20 min, and then centrifuged for 10 min at 23 °C. Serum was then frozen and stored at −80 °C until analysis at the Radioimmunoassay and Biomarkers Core of the Diabetes Research Center at the University of Pennsylvania. Gastrin concentration was measured by radioimmunoassay (Gastrin double antibody ^{125}I RIA kit MP Biomedicals, Santa Ana, CA). This assay was selected based on performance data from a previously published evaluation of gastrin assay kits [11]. The antibodies used in this kit bind both gastrin-17 and gastrin-34 and provided the correct diagnosis in 95% of patients with Zollinger–Ellison syndrome [11]. The normal value for fasting gastrin using this assay is <49.6 pg/ml.

2.4. Serum CgA analysis

Blood was collected in heparinized tubes, cooled in an ice-box, and centrifuged for 10 min at 4 °C. The serum was frozen and stored at −80 °C until analysis. CgA concentration was determined by radioimmunoassay by Euro-diagnostica [12]. Analysis was performed at the Clinical Central Laboratory at the Sahlgrenska University Hospital, Gothenburg, Sweden. The reference value for serum CgA using this assay is <6.0 nmol/l.

2.5. Helicobacter pylori tests

Testing for the presence of *H. pylori* infection in patients on PPIs is challenging because acid suppression can lead to false negative studies of active infection [13,14]. In addition, serologic testing is limited by an inability to reliably distinguish between active or past infection (the so-called serologic scar) [13,14]. We consequently performed both a previously validated ^{14}C-urea breath test (Heliprobe®,Kibion AB, Uppsala, Sweden) [15] and *H. pylori* serology (Serio ELISA classic *H. pylori* IgG sets, version 07/2010, Virion, Wurzburg, Germany) [16] on all study subjects.

Overall *H. pylori* status was determined as follows: if both the breath test and the antibody test were positive or negative, then the subject was labelled as being positive or negative for the infection, respectively. Patients with a positive breath test but negative serology were considered infected and those with a positive serology but negative breath test were considered infected if they had not undergone *H. pylori* eradication therapy but not infected if they had received prior therapy.

2.6. Statistical analysis

For processing the data IBM SPSS Statistics version 19 (IBM, Armonk, New York, USA) were used. Description of the data is given by medians and interquartile ranges. When comparing groups with dichotomous variables the Chi-squared test or Fisher exact test was used and for continuous variables the Mann–Whitney *U*-test was used. Kendall' correlation was used to evaluate associations between two variables [17]. If one variable is binary then the Kendall' and Mann–Whitney tests are equivalent. If, for example, females (F) are 0 and males (M) are 1 and the correlation coefficient was less than 0 (negative) then the gastrin values for M were lower on average than the gastrin values for F. When regression models were used for evaluating continuous outcomes the outcome variable was log transformed due to an uneven distribution of gastrin values. Multivariable logistic regression was used to identify independent predictors of baseline gastrin over the upper limit of normal (i.e., 49.6 pg/ml). Generalized linear models were used to identify predictors of the various gastrin and CgA levels. All reported *p*-values are two-tailed. The level of significance was set at 0.05.

The study was approved by the Bioethics Committiee of Iceland and all participants provided written informed consent.

3. Results

3.1. Participants

A total of 100 patients and 50 controls participated in the study and underwent meal stimulated gastrin measurements. Table 1 shows a comparison of the baseline demographics and other characteristics between the patients and the controls. No significant differences in terms of gender, smoking and alcohol consumption were noted. The patient group had a slightly higher median age and BMI.