Akin Oyalowo
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Tapered Withdrawal of a Proton Pump Inhibitor to Prevent Rebound Acid-Related Symptoms

A. Study Purpose and Rationale

Proton pump inhibitors (PPIs) are among the most commonly used medications in the US, and the use of PPIs continues to increase. Several patients are placed on these medications, often without clear indication, and many continue to take these medications on a daily basis for years. Proton-pump inhibitor therapy is now being prescribed for a wide variety of upper gastrointestinal symptoms on the basis that these symptoms might be acid-induced and thus may benefit from such treatment. Several factors have led to increasing use of these agents, including reduced concerns about potential side effects, reduced cost, and the lack of alternative therapies for upper gastrointestinal symptoms. This liberal employment of proton-pump inhibitor therapy has been recommended recently by many national and international guidelines based on "number needed to treat" and health economic analyses.[1] PPIs are also available over the counter (OTC). As a consequence, a substantial proportion of patients now prescribed proton-pump inhibitor therapy may not have acid-related symptoms and therefore have no true indication for such therapy. This is complicated by the observation that many clinicians and patients find it difficult to discontinue therapy due to the recurrence of symptoms after cessation of the drug.[2,3]

Previous clinical studies have shown that withdrawal of PPI therapy is difficult to achieve, possibly due to recurrence of the underlying acid-related disease but also as a result of physiologic changes triggered by PPI therapy itself.[3-6] Two recent double-blinded placebo-controlled trials have shown that a significant proportion of healthy, asymptomatic subjects who take a PPI for several weeks develop dyspeptic symptoms 1-2 weeks after discontinuing PPI therapy.[7,8] These recent studies suggest that these drugs may actually induce symptoms themselves, essentially causing patients with no previous need for such therapy to require intermittent or long-term treatment. Many investigators attribute this effect to a phenomenon described as rebound acid hypersecretion.[9,10] A plausible mechanism is the induction of hypergastrinemia due to PPI-mediated hypochlorhydria, leading to the hypertrophy of gastrin-sensitive enterochromaffin-like cells. By raising intragastric pH, proton-pump inhibitor therapy produces a substantial increase in the circulating gastrin concentration. Gastrin activates the cholecystokinin-2 receptor on the enterochromaffin-like cells, causing them to release histamine, which then acts on the H2 receptor of the parietal cell, thereby stimulating acid secretion. Upon withdrawal of PPIs, rebound acid hypersecretion may lead to acid-related symptoms.[1]

Though there is increasing evidence that PPIs may actually induce dyspepsia, little is known about the clinical significance of this effect, if any. The recent studies that were performed in asymptomatic patients had no long-term follow-up. Similar studies have been performed in patients who had an indication for starting PPI therapy (e.g., gastroesophageal reflux disease), but these studies have shown either no statistically significant rebound effect or are complicated by the fact that relapse of symptoms may be due to underlying disease, rather than a PPI-induced effect.[3,11] Furthermore, the recent randomized controlled trials do not demonstrate whether these dyspeptic symptoms last long-term, as the post-treatment symptoms that occurred were still present at the completion of both studies.

The purpose of this study is to determine the effectiveness of a tapered withdrawal of PPI therapy in order to reduce the incidence of acid-related symptoms after discontinuation of the drug. This study also aims to observe the long term effects of initiating and then discontinuing PPI therapy.

B. Study Design and Statistical Analysis

This study will be a prospective, randomized, placebo-controlled clinical trial to evaluate the effect of tapered withdrawal of omeprazole on development of clinically relevant acid-related symptoms after discontinuation of drug.

Initial Treatment Phase: At the beginning of the study, all enrolled patients will receive oral omeprazole 40 mg for 6 consecutive weeks. A weekly questionnaire will be completed starting prior to initiation through the completion of the entire study.

Study Arms: After the initial 6 week period, participants will then be randomly assigned to receive either:

a. Oral omeprazole 40 mg daily for 16 weeks
b. Oral omeprazole 40 mg for 1 week, omeprazole 20 mg for 1 week, omeprazole 10 mg for 1 week, omeprazole 10 mg every other day alternating with placebo for one week, followed by placebo for 12 weeks
c. Placebo once daily for 16 weeks

Number of subjects: Statistical analysis will be performed by means of a Chi-squared test for the categorical outcome of presence or absence of clinically relevant acid-related symptom. In order to achieve 80% power with an alpha-error rate of 0.05, a sample size of approximately 175 in each arm was calculated using the Chi-squared test, assuming a rebound effect of 45% in those on placebo for 16 weeks versus a rebound effect of for 30% of those in the tapered withdrawal arm. To allow for an attrition rate up to 12.5%, 200 subjects will be recruited into each arm of the study.

Randomization: Subjects will be randomly assigned consecutively (1:1:1 ratio) to one of three treatment arms once eligibility is confirmed and baseline assessments are completed. A clinical research coordinator will dispense the active medications or placebo to each participant in a computer-generated randomization. The placebo and active drug will be identical in appearance, shape, color, smell, and taste. All participants and study personnel will be blinded to treatment assignment. Subjects will not be crossed over from one group to another.

Primary Outcome Measures: presence or absence of clinically relevant acid-related symptom, determined by a GSRS score of >2 on one of the questions regarding heartburn, acid regurgitation, or dyspepsia.

Secondary Outcome Measures: duration of symptoms in those who report clinically relevant acid-related symptom

C. Study Procedure

Healthy volunteers without acid-related disease or symptoms will be chosen as our study population to establish that the symptoms observed were actually symptoms caused by the acid rebound phenomenon and not relapse of symptoms of underlying disease after discontinuation of treatment.

Participants will complete the disease-specific Gastrointestinal Symptom Rating Scale (GSRS) once a week on the same weekday throughout the study starting at baseline (week 0). The GSRS is a 15-item instrument combined into 5 symptom clusters depicting Reflux, Abdominal pain, Indigestion, Diarrhea, and Constipation. The GSRS uses a 7-point, Likert-type scale with 1 representing absence of bothersome symptoms and 7 representing very bothersome symptoms. The scores are calculated by taking the mean of the items completed within an individual scale. Respondents rate the severity of symptoms over the past week. The reliability and validity of the GSRS are well documented for use in measuring a range of gastrointestinal symptoms and disorders including gastroesophageal reflux disease and dyspepsia[12]. A score of >2 on 1 of the questions regarding heartburn, acid regurgitation, or dyspepsia is defined as a clinically relevant acid-related symptom.

All patients in the study will receive omeprazole. For the first 8 weeks, all patients will receive omeprazole. After 8 weeks, the patients will be randomized into one of three groups: continued PPI therapy at maximal dose, continued PPI therapy with taper over 4 weeks then placebo for 12 weeks, or placebo for 16 weeks.

D. Study Drugs

Omeprazole is a proton pump inhibitor. Its mechanism of action occurs via binding to H+/K+-exchanging ATPase (proton pump) in gastric parietal cells resulting in blocking acid secretion. Side effects include headache or abdominal pain. It is possibly associated with increased incidence of Clostridium difficile-associated diarrhea. Published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine; particularly with prolonged (>1 yr), high-dose therapy. Hypomagnesemia may also occur with prolonged use (ie, >1 year).; adverse effects may result and include tetany, arrhythmias, or seizures.

E. Medical Device

N/A

F. Study Questionnaires

Gastrointestinal Symptom Rating Scale (GSRS). The GSRS is used to diagnose the severity of gastrointestinal symptoms and to determine treatment for patients suffering from such symptoms. The GSRS is based on ratings for common gastrointestinal symptoms, including abdominal pain, constipation syndrome, diarrhea syndrome, indigestion syndrome and reflux syndrome.

G. Study Subjects

Inclusion Criteria:
-Healthy volunteers
-Male or female age 18 years or older

Exclusion Criteria:
-Suffered from dyspepsia, heartburn, or acid regurgitation 4 weeks before enrollment
-Positive H. Pylori test
-Previously used H2-blockers or PPIs
-Previous surgery in the upper abdomen
-Regular use of nonsteroidal anti-inflammatory drugs, antacids, antidepressants, or analgesics

H. Recruitment of Subjects

All study participants will be recruited from Columbia University Medical Center, the Allen Hospital and schools affiliated with Columbia (e.g. Medicine, Dental, Nursing, etc.). Primary care physicians will be notified of potential study participation and asked their opinion on patient's suitability for the study.

I. Confidentiality of Study Data
Upon randomization, all participants in the study will receive a unique study code number. Personal identifying information, including hospital unit numbers, social security numbers, subject names/initials, phone numbers, and addresses will be removed. The information used in the study will be stored in a secure database, accessible only to the investigators.

J. Potential Conflict of Interest
There is no potential conflict of interest to disclose.

K. Location of the Study
This study will take place at Columbia University Medical Center and the Allen Hospital.

L. Potential Risks
Risks associated with participation in the study include potential side effects of the study drug, documented above in the section entitled *Study Drugs*.

M. Potential Benefits
Potential benefits include determining whether dyspeptic symptoms after PPI discontinuation can be minimized or eliminated.

N. Alternative Therapies
N/A

O. Compensation to Subjects
Subjects will be compensated $50 for participation in the study. Payment will be given at completion of the study by check, which will be mailed to subjects. Participants who are unable to complete the study will receive a prorated amount.

P. Costs to Subjects
There will be no costs to subjects in this study.

Q. Minors as Research Subjects
Minors will be excluded from the study.

R. Radiation or Radioactive Substances
N/A

References

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