Questions concerning the connection between acid-related symptoms and commonly prescribed proton pump inhibitors have gastroenterology researcher Professor Peter Bytzer examining the clinical significance of this medical phenomenon and innovating trials to improve patient care.

What are the primary outcomes you hope to achieve through your investigations into acid rebound?

After a series of clinical and epidemiological studies, we hope to unravel the clinical significance, if any, of rebound acid hypersecretion (RAHS) in various patient populations. Patients with acid-related symptoms, such as heartburn and dyspepsia, are extremely common, and 10-20 per cent of all adults regularly use medication to alleviate these symptoms.

Can you explain what RAHS is and describe how it is caused?

RAHS is an increase in the secretion of gastric acid to above pre-treatment levels, which occurs following the withdrawal of proton pump inhibitors (PPIs), whose purpose is to reduce the amount of acid made by glands in the lining of the stomach.

Primary care physicians experience great difficulties when trying to help patients withdraw from PPIs, because this gastric acid-suppressive medicine interrupts the negative-feedback mechanism inherent in the body’s acid secreting system by blocking the proton pumps in the parietal cells. During long-term acid suppression, the lack of gastric acid leads to increased levels of gastrin and increased growth of enterochromaffin-like cells. When acid-suppressive medicine is withdrawn, the enlarged levels of gastrin and histamine result in acid secretion at a higher level than before the patient received treatment.

How does the withdrawal of PPI contribute to RAHS, and what are the long-term implications of continued withdrawal?

RAHS may contribute to the increase in long-term PPI therapy, as the increase in acid production may lead to acid-related symptoms when therapy is discontinued, thereby motivating patients to start PPI again. However, studies regarding the symptoms attributed to RAHS after PPI therapy have shown conflicting results, and have differed in study design and population sample. It is debated whether or not RAHS actually contributes to the difficulties in stopping PPI treatment, sparking concerns about maintaining unnecessary long-term treatment capable of causing medical and socioeconomic consequences.

What is your hypothesis regarding the treatment of functional dyspepsia (FD), and what research methodologies have you employed to validate your claims?

Patients with FD, which is characterised by an upset stomach or pain and discomfort in the upper belly, are often prescribed empirical PPI therapy, despite the fact that the therapeutic gain is close to that of a placebo treatment, especially for patients without coexisting heartburn. If RAHS occurs in FD patients, they may develop true acid reflux or even gastroesophageal reflux disease when they try to withdraw from treatment and consequently develop the need for further PPI therapy. This could lead to long-term PPI use, caused by acid rebound. However, it is not known how patients with FD respond to RAHS. In a randomised, controlled, double-blind withdrawal trial, we have investigated the signs and symptoms related to acid rebound in patients with FD who are treated with a PPI or placebo for eight weeks.

Could you outline the strengths and weaknesses of the trial’s design?

It is a major strength that the study is double-blind and that there is no risk of un-blinding due to side effects from PPIs. Furthermore, the patients are not informed of the general design of the trial. However, the symptoms of acid rebound may occur at any time during the first month after the withdrawal of the PPI, which complicates planning of invasive procedures (endoscopy and oesophageal pH-metry) that are necessary to detect lesions and RAHS-related acid reflux.

PPIs are often overused in hospitals and in primary care. How do you plan to address this problem through intervention studies?

The vast majority – 97 per cent in Denmark – of all PPIs are prescribed in primary care by family physicians. However, hospital doctors also readily prescribe PPIs for a variety of indications and generally, this prescription has no attached time limit. We hope that intervention trials in hospitals, where pharmacists scrutinise indications for new PPI prescriptions, will help minimise its use in patients without an obvious indication.
GASTRIC ACID IS crucial for digestion. Its formation relies on the parietal cells lining the stomach, which contain proton pumps in their membrane, also called the hydrogen potassium ATPases. These pumps transport hydrogen ions out from the cytoplasm of the cell in exchange for potassium ions from the gastric lumen in order to acidify stomach contents.

However, in many diseases, including peptic ulcers and gastroesophageal reflux disease (GERD), stomach acid can be damaging, and acid reflux is a relatively common complaint among the general population. In these conditions, proton pump inhibitors (PPIs) are often prescribed to inhibit its secretion, helping to alleviate the related symptoms. Although the incidence of acid-related conditions has remained stable, the use of these drugs has dramatically increased since they were first marketed in the 1980s. In particular, there is a growing number of people taking PPIs long term.

WITHDRAWAL SYMPTOMS
An emerging body of evidence suggests that such extended periods of use can cause the stomach to produce even more acid, a phenomenon called rebound acid hypersecretion (RAHS). When medication is terminated, a surge of acid can exacerbate, or even cause, symptoms such as heartburn and dyspepsia. Thus, many physicians report significant difficulties in encouraging patients to stop using PPIs. Professor Peter Bytzer of the Department of Clinical Medicine at Copenhagen University and Køge University Hospital is investigating RAHS, conducting a range of clinical and epidemiologic studies to determine its clinical significance. Bytzer believes acid rebound may be partially responsible for the increasing use of PPIs, which are used by 10 per cent of the population in his native Denmark.

Indeed, research conducted by Bytzer’s team has shown that RAHS can even generate symptoms in healthy individuals. In a recent trial, healthy participants were assigned 12 weeks of treatment with placebo, or eight weeks of PPI followed by a double-blinded shift to placebo for the final four weeks. Almost half of the group treated with PPIs suffered a significant increase in reflux symptoms following the shift, findings which have corroborated by a recent Swedish trial. Bytzer’s group hypothesise that a similar phenomenon might cause patients on long-term PPI therapy to resume medication after attempting withdrawal due to RAHS-induced symptoms. This study reveals a hidden aspect of PPI withdrawal and suggests RAHS could even lead to drug dependency.

CREATING PROBLEMS
The majority of patients without reflux disease on long-term PPI treatment suffer from functional dyspepsia (FD): impaired digestion without any underlying structural disease. In these cases, PPIs are generally no more effective than a placebo. In fact, Bytzer’s team believes that treatment of FD with PPIs may cause symptoms that were not present in the first place. This would clearly complicate therapy withdrawal, possibly encouraging the long-term use of PPIs in this group.

In order to evaluate the prevalence of this problem, Bytzer is leading the ‘CLinical trial of Acid Rebound In Functional dyspepsia’, or CLARIFY, study. “We recruit patients with FD from primary care physicians. These patients are often prescribed a PPI on an empiric basis,” he explains. At the beginning and end of this double-blind, randomised, controlled study, the researchers will analyse evidence of acid rebound symptoms through validated questionnaires and evidence of GERD using endoscopy and oesophageal pH-monitoring.
INTELLIGENCE

THE CLINICAL SIGNIFICANCE OF ACID REBOUND

OBJECTIVES

• To demonstrate the clinical significance of long-term treatment with proton pump inhibitors (PPIs) inducing gastric acid rebound after withdrawal in patients with acid-related disorders

• To evaluate if acid rebound may be partly responsible for the increasing use of PPIs

KEY COLLABORATORS

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PETER BYTZER earned his MD and his PhD in Medical Gastroenterology at Odense University Medical School, Denmark. He attended postgraduate medical and scientific training in Denmark, as well as in Sydney, Australia. Bytzer has been a national and international principal investigator in numerous clinical trials in peptic ulcer disease, dyspepsia, gastroesophageal reflux disease, inflammatory bowel disease and irritable bowel syndrome. Professional memberships include the American Gastrointestinal Association (fellow) and the European Association of Gastroenterology and Endoscopy. Since 2007, Bytzer has been Head of Department of Gastroenterology, Køge University Hospital, and since 2013, he has been Head of Gastroenterology and Hepatology at Copenhagen University.

ONLINE ASSESSMENT

Although the majority of PPI users are prescribed the medication by their local primary care practice, many patients purchase them over-the-counter. In order to assess this more casual form of PPI use, Bytzer and his team led a series of ‘webpanel’ studies designed for the general population. Based on an internet survey, the team mapped the usage patterns of different treatments for acid-related symptoms, qualified antacid/alginate and PPI users, and studied the characteristics that differentiate over-the-counter, short-term and long-term PPI users in Denmark.

The survey was conducted in 2012 and again, in the same population, one year later. The preliminary results show that nearly 15 per cent used PPIs, with around half of these being long-term users. Generally, antacid/alginate users were younger, begun therapy due to reflux and had fewer ongoing symptoms. The researchers found the risk of long-term PPI use was higher in males, those who renewed prescriptions by phone or email, and individuals using co-medication. In a follow-up study, the results of which are yet to be published, researchers focused further on identifying predictors for long-term PPI use and the characteristics of those patients who attempt to stop using them.

SURGICAL COMPLICATIONS

PPI therapy is not the only option for reflux disorders, and some people with GERD receive recommendations of anti-reflux surgery (ARS) as an alternative. This most often comes in the form of ‘laparoscopic fundoplication’, where the upper curve of the stomach is wrapped around the oesophagus to strengthen the sphincter between the two, stopping acid from entering the oesophagus and enabling it to heal. However, the factors used to recommend ARS are highly debated, as Bytzer reveals: “Some argue for a conservative approach, restricting ARS to tightly selected patients, such as those with regurgitation poorly controlled by PPI. However, it has also been suggested that ARS is beneficial for patients successfully treated with PPI, but who have a desire to stop using them for financial, social or health-related reasons”.

Clinical trials have shown that, following ARS, the use of PPIs is minimal, with the majority of studies showing less than 25 per cent of patients using the drugs up to 12 years following surgery. “However, there may be discrepancies between what can be observed in controlled clinical trials and what is observed in a nationwide context, where patients are treated outside these rigid frameworks,” Bytzer notes. To reconcile these differences, he investigated PPI use following ARS in the general population, using nationwide healthcare registries.

This retrospective study of over 3,000 patients revealed startling differences to previous reports. The results showed that PPIs were used by over 50 per cent of ARS patients five years after surgery, and by a massive 80 per cent within 15 years. The overall risk of becoming a long-term PPI user was over 50 per cent, suggesting that scientists and medical professionals should evaluate ARS’s effect on reflux symptoms more cautiously. This finding could have important implications for clinical practice, and it has led Bytzer to recommend that medical professionals make all patients aware that PPI therapy is often necessary following ARS.

PROPER USE

The final aspect of Bytzer’s work on acid rebound is focused on PPI overuse, particularly in hospitals and primary care facilities. In their initial investigations, the team found that decisions to initiate PPI therapy during hospital admission slide through into primary care. “Many patients return from a stay in hospital to their family physician with a prescription for a PPI, which the family doctor does not dare to question,” Bytzer expands. In order to prevent long-term PPI therapy, the team will now conduct intervention trials, comparing long-term outcomes between an ‘intervention hospital’, where decisions are made by trained pharmacologists, and a control hospital, with no planned interventions.

Already, the team has made significant progress. They have shown that just eight weeks of PPI treatment in healthy volunteers induces acid-related symptoms that were not present when the individuals started taking the medication. This strongly supports the concept of RAHS-induced symptoms and suggests that PPI therapy may actually induce the symptoms it is meant to treat. Given the huge clinical ramifications, Bytzer plans to investigate RAHS in much more depth: “We hope our clinical trials and pharmacoepidemiologic studies will shed further light on the clinical relevance of acid rebound following PPI therapy”.

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