The failure of Proton Pump Inhibitors in Gastro Esophageal Reflux Disease

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Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Observational invasive

Summary

ID

NL-OMON35604

Source
ToetsingOnline

Brief title
PPI failure

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
GERD, heartburn

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Acid pocket, Gastro esophageal reflux disease (GERD), Proton pump inhibitor (PPI)

Outcome measures

Primary outcome

Primary study outcome:

- The position of the postprandial gastric acid pocket relative to the

esophagogastric junction

Secondary outcome

Secondary study outcomes:

- Esophageal sensitivity for distension and chemical stimuli (VAS scores)

- Concentration of Bile acids in the gastric acid pocket

- The rate of postprandial acid reflux events

- The size of the postprandial acid pocket

- The acidity of postprandial reflux events

- The acidity of the postprandial gastric acid pocket

- Histology of the esophageal mucosa

- Permeability of the esophageal mucosa

Study description

Background summary

Gastro-esophageal reflux is a common phenomenon in which gastric contents flow back into the esophageal lumen. When reflux causes symptoms and/ or esophageal damage, it is referred to as gastro esophageal reflux disease (GERD). Proton pump inhibitors (PPIs) are widely used in the treatment of GERD. PPIs diminish the secretion of acid by blocking the H+/K+ ATPase pump of the parietal cells of the stomach. In approximately 30% of patients PPI-therapy fails to

completely resolve symptoms, either partially of completely. Additionally, it appears that less than 50% of patients with GORD are satisfied with their medical treatment, and only 58% of those receiving PPIs report a high level of satisfaction with it. The group of patients with GERD with partial PPI failure is a clinical problem, as there is only limited additional medicinal therapy, and antireflux surgery can lead to serious morbidity.
It is unknown what causes the failure of PPIs in this group of patients. After exclusion of patients with a wrong diagnosis and incompliant patients, several factors are proposed:
1. Increased sensitivity: Treatment with PPI changes the pH of the refluxate, but leaves the amount of reflux episodes unaffected. An increased sensitivity for weakly acid reflux might explain symptoms. Two possible explanations are proposed: hypersensitivity for distension of the upper esophagus, or hypersensitivity to chemical stimuli.
2. Increased permeability: The permeability of the esophageal stratified mucosa is shown to be increased in GERD patients, by means of the dilated intracellular spaces. An increased esophageal permeability enables refluxate to reach the nerves in the esophageal mucosa. It is proposed that patients who remain symptomatic during PPI treatment have dilated intercellular spaces.
3 Chemical composition of refluxate: Refluxate contains several potentially noxious factors, of which H+ is the only factor affected by PPIs. It is already shown that a significant portion of symptoms during PPI treatment are actually caused by reflux of bile acids.
4 Position of the gastric acid pocket In recent work of our group we have shown the importance of the gastric acid pocket, a pool of acid floating on top of a meal, for the occurrence of acid reflux. By injection of 99mTc-pertechnetate we were able to visualize this pool of acid scintigraphically. This pocket is also present during PPI therapy, and therefore we hypothesize that the position and other properties of the postprandial acid pocket differ in patients with refractory symptoms compared to patients with good clinical response.
These 4 factors are proposed as factors that influence proton pump failure; however they have never been examined in patients with proton pump failure versus patients with good clinical respons.

Study objective

In this study we aim to determine the esophageal sensitivity by means of weakly acidic solution and esophageal distension, and determine the position and composition of the acid pocket in patients with and without PPI. We hypothesize that these factors influence the (partial) failure of PPIs in patients with GERD and might enable us to better target therapy beyond PPI in the future.

Study design

The study has a prospective cross sectional design.

Intervention

stop medication for 1 week

Study burden and risks

Risks and Burden:
Oesophagogastroduodenoscopy
Upper endoscopy is a routenily performed investigation, which belongs to the standard procedures in patients with GERD. In this short investigation the esophagus, stomach and proximal duodenum are watched with an endoscope. During endoscopy, patients will be placed on a monitor that checks heart rate, blood pressure and oxygen level.
Esophageal biopsies are taken regularly during upper endoscopy. A possible severe risk of a biopsy is a perforation (0,03%). In most cases perforation can be treated expectative or endoscopically. In a minority of cases, surgery has to be perfomed to close the perforation. Another risks of esophageal biopsies is bleeding, which can be treated endoscopically.
Scintigraphy
During studay 2 350 MBq 99mTc-pertechnetate is applied intravenously. 99mTc-pertechnetate has no known side effects other then the radiation. The radiation dose is in the intermediate category. Patients who recently participated in a trial with radiation are excluded from the trial.
All study days have the burden of introduction of catheters or an endoscope. furthermore patients have to stop using PPI for one week.

Group relatedness and benefit.
The patients studied all have proven reflux disease. Patients do not benefit from participation in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

GERD patients with good symptom response to PPI:
- Written informed consent
- 18-75 years
- PPI use of 1-2 daily 40 mg of Omeprazole, Esomeprazole or pantoprazole, or 1-2 daily 30 mg of lansoprazole.
- GERD confirmed by pH-impedance (ph<4 in > 4,5 % of time or positive symptom association), or in patients with reflux esophagitis.;GERD patients with bad symptom response to PPI:
- Written informed consent
- 18-65 years
- PPI use of 1-2 daily 40 mg of Omeprazole, Esomeprazole or pantoprazole, or 1-2 daily 30 mg of lansoprazole.
- GERD confirmed by pH-impedance during medication, with a positive symptom association between reflux episodes and symptoms (Symptom Index >50%, or a Symptom Association Probability >95%).

Exclusion criteria

- surgery of the gastrointestinal tract other then appendectomy
- inability to stop the use of proton pump inhibitors for one week
- participation in another study with exposure to radiation within the last year
- long segment of Barrett*s epithelium

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2010
Enrollment:	24
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL29580.018.10