Ziverel for PPI-refractory reflux symptoms: efficacy and mechanisms of action in humans

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To assess the effect of Ziverel on esophageal sensitivity to acid, mucosal barrier function and reflux symptoms in patients with PPI-refractory reflux symptoms.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Interventional

Summary

ID

NL-OMON46254

Source
ToetsingOnline

Brief title
Ziverel for refractory reflux symptoms

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
Heartburn, pyrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Heartburn, Pyrosis, Reflux, Ziverel

Outcome measures

Primary outcome

The main study parameter is the perfusion sensitivity score (acid perfusion test).

Secondary outcome

Secondary endpoints are (1) symptom score improvement based on the RDQ Questionnaire score, and (2) esophageal barrier function measured with Ussing chamber experiments and electrical tissue impedance spectroscopy during endoscopy.

Study description

Background summary

Approximately one third of the patients with gastroesophageal reflux disease (GERD) has refractory symptoms despite daily proton pump inhibitor (PPI) use. Several studies have suggested that an impaired mucosal barrier function might underlie symptom perception and esophageal acid sensitivity, and thus contributes to PPI-resistant symptoms. Therefore, impaired mucosal barrier function is considered a potential therapeutic target in reflux disease.
Ziverel is a medical device that consists of hyaluronic acid and chondroitin sulphate. It is a bio-adhesive formulation with tissue regenerating abilities that coats the esophageal wall and thereby acts as a mechanical barrier against the noxious components of refluxate. One ex vivo study model in pigs demonstrated that Ziverel prevents acid perfusion-induced mucosal barrier damage in the esophagus, but these effects still have to be confirmed in humans. It has been demonstrated in prior studies that Ziverel combined with PPIs indeed provided superior control of reflux symptoms in GERD patients compared to placebo. However to date, this only has been investigated in a limited number of studies and the underlying working mechanism in humans has not been elucidated yet. Hence, more information on efficacy and mechanisms of

action is warranted.

Study objective

To assess the effect of Ziverel on esophageal sensitivity to acid, mucosal barrier function and reflux symptoms in patients with PPI-refractory reflux symptoms.

Study design

A prospective CE-marked medical device study with a double blind placebo-controlled, randomized cross-over design.

Intervention

Patients will receive the first period either a placebo or Ziverel four times daily for 14 days, followed by a second period in which they will receive the other study medication. There will be a washout period (at least 14 days) in between the two treatment periods. At the end of the two 14-day treatment periods questionnaires are filled in, patients will undergo an upper endoscopy with electrical tissue impedance spectroscopy and biopsy sampling for ex vivo Ussing chamber experiments and an esophageal acid sensitivity test (modified Bernstein test) will be performed. Patients will continue 2 times daily standard dose of PPI for the entire duration of the study.

Study burden and risks

The subjects will have a total of three visits and will have to fill out questionnaires on three separate occasions. Patients undergo two upper endoscopies with biopsy sampling and two esophageal acid perfusion tests. Both endoscopy and acid perfusion test cause mild discomfort. Sedation can be provided on demand. Risk of perforation or bleeding of biopsy taking is smaller than 1/10000 endoscopies. Participants will be compensated financially for participation in the study and the findings could help treat future patients with similar complaints.

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

- Age above 18 years
- Symptoms of heartburn and/or acid regurgitation under PPI treatment for at least 3 months.
- Use of proton pump inhibitors at a standard two times daily dose for at least 4 weeks prior to inclusion, same dosage should be maintained during the entire study period.

Exclusion criteria

- Previous gastric or major gastrointestinal surgery other than appendectomy or cholecystectomy.
- Use of any other medication than proton pump inhibitors with a potential effect on gastrointestinal motility, secretion or sensitivity that cannot be stopped for the duration of the study (e.g. H2-blockers, antidepressants, prokinetics, antacids)
- Known Barrett*s esophagus
- History of gastrointestinal cancer
- Known allergy to one of the ingredients of Ziverel
- Severe and clinically unstable concomitant disease (e.g. liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders)
- Pregnant, lactating or fertile women (without contraception)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-09-2019
Enrollment:	22
Type:	Actual

Medical products/devices used

Generic name:	Ziverel
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	24-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2019
Application type:	Amendment
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	NL66698.018.18