The absorption of non-haem iron during suppression of gastric acid secretion

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A close correlation has been demonstrated between iron absorption and the capacity of gastric juice to release food iron. At high levels of gastric pH (>3,6), negligible amounts of non-haem iron would be released from dietary components and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary disorders congenital
Study type	Interventional

Summary

ID

NL-OMON41064

Source
ToetsingOnline

Brief title
The absorption of non-haem iron and gastric acid

Condition

- Hepatobiliary disorders congenital
- Gastrointestinal conditions NEC
- Hepatic and hepatobiliary disorders

Synonym
hereditary hemochromatosis, iron overload disease

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: nvt

Intervention

Keyword: absorption, gastric acid suppression, non-haem iron, proton pump inhibitor

Outcome measures

Primary outcome

The course in hepcidin concentration, measured after an oral iron challenge, before and after gastric acid suppression in hemochromatosis patients and healthy controls will be the primary endpoint of the study.

Secondary outcome

The secondary endpoint is to prove the difference in increase of serum iron concentration, after oral iron challenge, before and after gastric acid suppression in hemochromatosis patients and healthy controls.

Study description

Background summary

Food is the most common source for iron, in which it can be found as non-haem or haem iron. Non-haem iron enters the enterocytes via the divalent metal transporter 1 (DMT-1) located in the apical membrane of enterocytes. This transporter is selective for ferrous iron (Fe2+), making a reduction step of ferric iron (Fe3+) necessary, because dietary iron is in the ferric form. Non-haem iron supplies at least two thirds of dietary iron requirements. Gastric hydrochloric acid (HCl) acts to promote the optimum absorption by reducing ferric iron (Fe3+) to the more soluble ferrous form (Fe2+). Hereditary hemochromatosis (HH) is a genetic disorder of iron metabolism resulting in excessive iron overload causing damage of different important organs such as liver, heart, pancreas and joints. It has been suggested that iron accumulation in most types of hemochromatosis is due to deficiency of hepcidin, a central iron regulator.

Study objective

A close correlation has been demonstrated between iron absorption and the capacity of gastric juice to release food iron. At high levels of gastric pH

(>3,6), negligible amounts of non-haem iron would be released from dietary components and reduction of ferric iron and formation of ferric chelates would be impaired. This would have a major impact on iron absorption. In an open observational open study, Hutchinson et al found that administration of a proton pump inhibitor (PPI) to patients with hereditary haemochromatosis gives a significant reduction in the maximum increase in serum iron concentration following ingestion of a test meal, containing highly bioavailable iron. However, long-term use of PPI has not been reported to compromise iron status in normal subjects.
Since PPI therapy is very common, we foresee within short notice an expansion of PPI prescription in (hemochromatosis) patients. Thus structured evaluation of the mechanism behind reduction in increase of serum iron after an oral iron challenge during gastric acid suppression is mandatory.
How can the difference in iron absorption between hemochromatosis patients and healthy controls be explained? We hypothesize that due to diminished gastric acid production the reduction step of ferric to ferrous iron will be reduced; as a consequence the hepcidin concentration in HCs decreases, after gastric acid suppression, to compensate for the reduced availability of ferrous iron (Fe2+).

Study design

A nonrandomized study among hemochromatosis patients and healthy controls on the effect of gastric acid suppression on serum iron and hepcidin concentration. After a test dose of ferric iron, the course of the parameters will be studied in both the hemochromatosis patients and healthy controls.

Intervention

After an overnight fast serum iron and hepcidin concentration will be determined. Healthy controls and hemochromatosis patients will then receive iron (Fe3+) polymaltose containing 50 mg of iron, the standard advised dose of oral liquid. Serum iron will be measured hourly for 4 hours, and hepcidin concentrations are measured after 3 and 4 hours after ingestion of the solution. Then all the participants will use pantoprazole 40 mg daily for a week, after which they will have iron polymaltose again and the same parameters are measured.

Study burden and risks

At inclusion a history of the patient will be taken and a physical examination will be performed. Furthermore routine blood tests will be performed as depicted in the table. Besides a bruise, no side effects of the venepuncture are expected as patients will be sitting or lying down when undergoing venepunction. After an overnight fast, serum iron and hepcidin concentrations will be measured. Then the participants have to ingest iron polymaltose, after

which blood samples will be taken.
The participants will use a pantoprazole for a week, one tablet a day in the morning. Then the oral iron challenge will be repeated in the same way as before pantoprazole use.
Side effects of PPIs are rare. Possible side-effects (1-10%) are pain in upper abdomen, diarrhoea, constipation, flatulence and headache. Data of long term complications are sparse. Elevation of gastrin is found and can lead to expansion of enterochromaffin-like cells (ECL) without risk of carcinoma. In small studies bacterial overgrowth has been observed as a consequence of strong acid suppression. The patients have a slightly elevated change of bacterial gastrointestinal infection and pneumonia. Since the subjects only use the pantoprazole for one week, no side effects are expected.
Side effects of oral iron are mainly gastro-intestinal disturbances. Since participants will receive a small dose (50 mg) not on regular basis, little to none side-effects are expected.

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

In order to be eligible to participate in this study, a hemochromatosis patient must meet all of the following criteria:
• Patients with hereditary hemochromatosis, homozygous for C282Y, with biochemical or liver biopsy proven iron overload in the past.
• Patients are currently on maintenance treatment of which the last treatment was more than six weeks ago.
• Ferritin levels for men and postmenopausal women should be < 400 ug/l and for premenopausal women <150 ug/l, for at least 3 months.
• Age: > 18 years, <=65;A healthy control must meet all the following criteria:
• Subjects do not have HFE mutations
• Age >18, <=65
• Ferritine levels for men and postmenopausal women should be < 400 ug/l and for premenopausal women <150 ug/l.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Patients/subjects with known acute or chronic inflammatory disorders, such as inflammatory bowel disease or rheumatoid arthritis, hepatitis B, hepatitis C or HIV infection
• Patients/subjects with cirrhosis of the liver
• Patients/subjects with excess alcohol ingestion (> 21 glasses a week for men, >14 glasses a week for women)
• Phlebotomy/erythrocytapharesis less than 6 weeks before participation in research
• Patients/subjects <18 years, and >65 years
• Patients/subjects with a malignancy
• Patients/subject who are anemic
• Patients/subjects already on PPI treatment
• Patients/subjects who experienced side effects of PPI*s
• Patients/subjects on different acid-suppressing medication (e.g. H2- blockers)
• Patients/subjects that use iron supplements
• Patients/subjects who are pregnant.
• Patients/subjects who use medication that interferes with PPI medication.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-01-2015
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	25-09-2014
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	NL49850.096.14