Endoscopic Measurements of Mitochondrial Oxygen Tension: a dose-finding study

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* To determine the minimum effective dose of 5-aminolevulinic acid (Gliolan) for adequate MitoPO2 measurements during upper endoscopy.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal vascular conditions
Study type	Observational invasive

Summary

ID

NL-OMON44385

Source
ToetsingOnline

Brief title
Endo-mitoPO2-dose-study

Condition

- Gastrointestinal vascular conditions
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
chronic mesenteric ischemia, lack of oxygen of the intestine

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 5-aminolevulinic acid, chronic mesenteric ischemia, mitochondrial oxygen tension, upper endoscopy

Outcome measures

Primary outcome

the minimum effective dose of 5-aminolevulinic acid (Gliolan) for adequate

MitoPO2 measurements during upper endoscopy

Secondary outcome

not applicable

Study description

Background summary

Adequate oxygen supply to the tissues is a required condition for human life, moreover for life of all mammalians. Oxygen supply starts with inhaling of oxygen and subsequently the inhaled oxygen will be transported via the circulating blood to the tissues. Many pathophysiological mechanisms lead to insufficient oxygen supply: on one hand a decreased oxygen delivery due to for example a decreased cardiac output, obstruction of the blood flow, anemia or poor oxygenation, low flow state for example due to systemic vasodilatation in sepsis, on the other hand an increased metabolic demand in, for example, critically ill patients. Therefore, adequate and reliable measurements of tissue oxygenation are important for diagnosis and treatment decisions of a broad spectrum of diseases. Many techniques have been developed for oxygen measurements in vivo but the ultimate goal is to measure oxygen at the level where it is used by the mitochondria. Mik et al. introduced the protoporphyrin IX-triplet state lifetime technique (PpIX-TSLT) for measuring PO2 in mitochondria. The in vivo experiments with this technique of measuring mitochondrial oxygen (mitoPO2) were performed in animals and humans.

The technique resulted in the development of the COMET monitor, a clinical monitor for assessment of Cellular Oxygen METabolism, allows cutaneous mitoPO2 measurements to be made in humans. COMET measures mitoPO2 by means of the Protoporphyrin IX-Triplet State Lifetime Technique (PpIX-TSLT). Cutaneous application of 5-aminolevulinic acid (ALA) is necessary to induce enough mitochondrial PpIX for detection of the weak delayed fluorescence signal. Since

the first publication of this technique in 2006, extensive research has been done to develop an instrument for clinical use. The technique has been tested en calibrated for use in isolated organs and in vivo in experimental animals. The positive results of a feasibility test in healthy volunteers have been published.

This technique is recently tested in the stomach and small intestine during upper endoscopy in our center. We performed mitoPO2 measurements of the gastrointestinal tract. Possibly, mitoPO2 measurements can be used in the work-up of chronic mesenteric ischemia (CMI) in the future. CMI is the result of insufficient blood supply to the gastro intestinal tract. Three aortic branches provide the arterial blood supply of the gastro intestinal tract: the celiac artery (CA), the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA). Between these vessels is an extensive collateral circulation. The main cause of CMI is occlusive disease of one or more supplying arteries, most common due to atherosclerosis. In some cases, the mesenteric blood flow is diminished due to a non-occlusive cause like decreased cardiac output, hypovolemia and hypotension: non-occlusive mesenteric ischemia (NOMI).

The diagnosis of CMI remains a clinical challenge because this diagnosis is difficult to distinguish by the frequent incidence of chronic abdominal pain and asymptomatic stenosis of the mesenteric arteries, due the presence of abundant collateral circulation.
The standard diagnostic work up includes assessment of clinical symptoms, radiological imaging and a functional test6,7 as visible light spectroscopy (VLS) or tonometry. The diagnosis of CMI is based on three main components. The first main component concerns assessment of medical history, clinical symptoms and physical examination. Radiological imaging of the mesenteric arteries is the second component. Finally, the third component consists of detection of mucosal ischemia by a functional test. The sensitivity and specificity of VLS is respectively 90% and 60% with positive and negative predictive values of 88% and 67%, respectively. The sensitivity and specificity of 24-hours tonometry is respectively 76% and 94% with positive and negative predictive values of 76% and 94%, respectively. These three main components will be discussed in a multidisciplinary team consisting of a gastroenterologist, a vascular surgeon and an interventional radiologist, all specialized in CMI. This results in an expert-based consensus diagnosis.
If the patient fulfills two of the following criteria, the diagnosis CMI is made:
1. Distinctive clinical presentation including presence of postprandial pain and otherwise unexplained weight loss of >5% of the normal body weight.
2. Significant stenosis of >70% of at least one of the mesenteric arteries demonstrated by radiological evaluation.
3. Mucosal ischemia detected by tonometry or visible light spectroscopy (VLS).

When relief of symptoms is persistent after treatment, a definitive diagnosis

of CMI is made. In case of one-vessel disease, three of the above criteria has to be fulfilled for the diagnosis of CMI.

Concluding, current diagnostic work-up of CMI is quite a process with various investigations in the absence of just one specific test to diagnose CMI. There is need of a reliable non-invasive functional test for chronic mesenteric ischemia to assess the oxygenation of the gastrointestinal tract with high accuracy. The protoporphyrin IX-triplet state lifetime technique for measuring mitoPO2 in the skin, liver4 and heart is fast, non-invasive and reliable. Recently, we have proven he feasibility of endoscopic MitoPO2 measurements in healthy volunteers during a previous pilot-study in our center. However, these measurements were performed with a dose of 20 mg/kg 5-aminolevulinic acid (Gliolan). We recorded a very high signal of the 5-aminolevulinic acid induced PpIX, which means that a lower dose of Gliolan will be effective as well for adequate MitoPO2 measurements during upper endoscopy. Further, a lower dose of Gliolan will provide less dose-dependent side effects as photo toxicity.

Study objective

* To determine the minimum effective dose of 5-aminolevulinic acid (Gliolan) for adequate MitoPO2 measurements during upper endoscopy.

Study design

Inclusion
Healthy volunteers with no gastrointestinal complaints and unremarkable medical history will be asked to participate in our study through information folders in the Erasmus MC, Rotterdam. This folder will provide information about the study and the study procedure, and also how to contact the research investigator. If people are interested, they can contact the coordinating investigator for a consult to obtain further information. They will receive the patient information folder. If a healthy volunteer decides to participate in the study, he or she will sign the Informed Consent Form and blood sampling to exclude renal and liver impairment and the upper endoscopy will be scheduled.

Intervention
The healthy volunteers will drink 5-aminolevulinic acid (ALA, Gliolan 30 mg/ml) 4 hours before the upper endoscopy. The dose of Gliolan will be 0 mg/kg weight for the first volunteer and 1 mg/kg for the 2nd and third volunteer. If the signal of the 5-aminolevulinic acid induced PpIX is too low with 1 mg/kg, a 4th and 5th volunteer will be included an they will receive Gliolan with a dose of 5 mg/kg. If the signal of the 5-aminolevulinic acid induced PpIX is too low with 5 mg/kg, a 6th and 7th volunteer will be included and they will receive Gliolan with a dose of 10 mg/kg. Four hours after the administration of Gliolan the upper endoscopy will be performed.
Healthy volunteers can choose if they want sedation or not during the

endoscopy. Sedation will be 2.5-5 mg midazolam combined with 0.05 mg fentanyl intravenously prior to the endoscopy. The MitoPO2 measurements will be performed with the COMET measurement system during upper endoscopy using a sterile single use fiberoptic-catheter (MUCS000001, LightGuideOptics, Germany) that can be passed through the accessory channel of the endoscope. Measurements of the MitoPO2 will be performed at three sites in the stomach and duodenum: antrum of the stomach, descending duodenum and duodenal bulb. Three repeated readings will be taken at different areas of each location. The average of the three readings per location will be regarded as the actual measurement of that specific location. Furthermore, on each location the probe will gently pressed on the tissue to demonstrate the oxygen dependence of the measurements. To prevent luminal spasms butylscopalamin 20mg is admitted intravenously before the start of the measurements.

Afterwards, healthy volunteers with sedation will be brought to the endoscopy recovery room to sleep off. If no sedation is used, healthy volunteers are required to go immediately after the endoscopy. It is important to notice that they should avoid exposure to strong light sources (eg. direct sunlight or brightly focused indoor light) of eyes and skin for 24 hours after administration of Gliolan. The total duration of the upper endoscopy will be 15 minutes maximally.

Follow-up
There is no follow-up of the healthy volunteers in this study. Obviously, if during upper endoscopy findings are detected, the healthy volunteer will be referred to our outpatient clinic for further analysis and treatment.

Study burden and risks

An upper endoscopy with MitoPO2 measurements will be performed in healthy volunteers. The risks of upper endoscopy without invasive intervention are very low, especially when no sedation is used. Oral administration of Gliolan (for PpIX induction) is safe. The risk of phototoxicity after PpIX induction is considered low, because the COMET uses short-pulsed excitation and very low total light dosage. To limit the potential effects of phototoxicity, healthy volunteers will be instructed to avoid exposure to strong light sources (eg. direct sunlight or brightly focused indoor light) of eyes and skin for 24 hours after administration of Gliolan.

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

* * 18 years
* Informed consent
* Unremarkable medical history (no gastroenterologic diseases or surgery, no cardiac or pulmonal diseases)
* No gastrointestinal complaints

Exclusion criteria

* < 18 years
* Unable to give informed consent
* Pregnancy
* Acute or chronic porphyria
* Hypersensitivity for ALA or porphyrin
* Renal impairment (defined as estimated Glomerular Filration Rate (eGFR) < 90 ml/min/1.73m2)
* Liver impairment (defined as > 1.5x Upper Limit of Normal (ULN) of Alanine transaminase (ALT and/or Aspertate transaminase (AST) and/or alkaline phosphatase (ALP) and/or gamma-

glutamyltransferase (GGT) and/or bilirubin)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-03-2018
Enrollment:	7
Type:	Actual

Ethics review

Approved WMO

Date:	01-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL63050.078.17