Clinical pilot study to determine the feasibility of detecting pancreatic beta cells using Exendin-4-800CW targeting the glucagon-like peptide 1 receptor for future application of molecular fluorescence guided surgery in insulinoma patients (BETA-light)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46762

Source
ToetsingOnline

Brief title
Detecting beta cells with a fluorescent tracer (BETA-light)

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
Insulinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: FP7 project BetaCure

Intervention

Keyword: fluorescence, GLPR-1, imaging, pancreas

Outcome measures

Primary outcome

- Back-table imaging of the surgical specimen directly after excision to identify fluorescence signals of Exendin-800CW

- Correlation of fluorescence signals with histology.

- Calculating target to background ratios in fluorescence imaging obtained directly after the surgical procedure and fluorescence images obtained during ex vivo analyses in bread loaf slices and in histological slices (odyssey scanner, fluorescence microscopy).

- Adverse events (AE), serious adverse events (SAE), and suspected unsuspected serious adverse reactions (SUSARs).

Secondary outcome

-

Study description

Background summary

Reliable visualization of beta cells would benefit the optimization of treatment of patients with adult endogenous hyperinsulinemic hypoglycaemia

(AHH). By visualizing molecular changes that accompany disease, molecular imaging holds the promise to be able to better characterize disease states and extent at an earlier time and with lower required contrast differences than current (anatomical) imaging modalities. Tumour-specific intraoperative near-infrared (NIR) fluorescence techniques have two major advantages: they not only give visual feedback to the surgeons, but also provide quantitative measurements that can be analysed for the presence of positive margins and microscopic residual disease. Therefore, this novel approach could lead to a minimization of side-effects from the surgical treatment, decrease recurrence rates and ultimately improve disease free survival. Image guided surgery requires optical tracers with a considerably high target-to-background ratio in order to enable differentiation between diseased and healthy tissue. The glucagon-like peptide 1 receptor (GLP-1R) is overexpressed in insulinoma lesions, which is the main cause of AHH. Currently, the PET imaging agent 68Ga-NODAGA-exendin-4 is under investigation as preoperative diagnostic imaging agent which shows highly specific uptake in insulinoma lesions. Therefore, GLP-1R is considered to be a promising molecular target for intraoperative imaging as well. In this feasibility study, we would like to investigate if the fluorescent tracer exendin-4-800CW is targeting pancreatic beta cells for future optimization of surgery in patients with AHH.

Study objective

The primary objective is to determine if accumulation of the fluorescent tracer Exendin-800CW can be detected to identify beta cells in patients undergoing pancreatic resection. Secondary objectives are to identify the dose of the NIR peptide (Exendin-4) conjugate that provides the best visualization of beta cells and to obtain information on safety aspects of the tracer.

Study design

The current study is a non-randomized, non-blinded, prospective, single center pilot study. A total of 9 patients undergoing a pancreatic head or tail resection will be included. The trial will consist of 3 subject cohorts of 3 patients each. The doses for each consecutive cohort will increase from 7 µg to 14 µg and 30µg of the tracer Exendin-800CW. The tracer will be injected 24 hours prior to surgery. Following injection of the tracer all patients will be monitored at least 2 hours for side effects like nausea, vomiting, headache, dizziness and hypoglycemia for safety, even though side effects are not expected. To adequately monitor glucose levels, finger pricks will be performed just before injection and 15, 30, 60 and 120 minutes after injection of the tracer. Blood will be drawn at 1, 2, 4 and 24 hours after injection to asses pharmacokinetic data. After surgery, all patients will be monitored for at least 14 days. After every three subjects the next dose level cohort opens if safety outcomes (in terms of (S)AEs) with its following conclusions reveal that continuation to the following cohort is justified. A total of three cohorts

will be included; therefore, the number of subjects will be 9.

Intervention

A total of 9 patients will receive an injection of Exendin-800CW 24 hours before surgery. Directly after surgery the pancreatic tissue will be examined on the back-table and by image-guided pathology to identify fluorescent signals.

Study burden and risks

Time investment for study participants
Patients who are scheduled to undergo a pancreatectomy due to an insulinoma, another type of neuro-endocrine tumour or because of a suspected (adeno-)carcinoma are asked to participate in this trial. Once written informed consent is obtained the patient will receive the tracer 24 hours prior to surgery. No additional study specific visit to the UMCG is necessary.

Risks for study participants
All individuals will undergo physical examination and blood sampling for standard laboratory parameters. In addition, all patients will undergo the current standard preoperative care. Exendin-800CW will be administered 24 hours prior to surgery. Blood pressure and blood glucose levels will be measured just before and 15, 30, 60 and 120 minutes after injection of the tracer. Injection of the tracer may result in nausea and headache as has been reported for doses 10-100µg of Byetta® in therapy studies. In addition, a decrease of blood glucose levels (0.8 * 2.1 mmol/l has been described after injection of 8 * 14 µg 111In-DTPA-exendin-4 in patients with AHH (Christ E. et al. Lancet Diabetes Endocrinol 2013;1:115-22). Importantly, regular monitoring of glucose concentrations injection led to no serious episodes of hypoglycaemia. Therefore, no side-effects are anticipated with injection of Exendin-800CW, although patients will be closely monitored. Furthermore, a prophylactic glucose infusion (5% glucose for 2 hours at 250 ml/h) will be started 15 minutes before injection of Exendin-800CW. Finally, to receive pharmacokinetic data about the tracer, blood samples will be taken at 1, 2, 4 and 24 hours after injection. Since the patient receives a prophylactic glucose infusion, it is possible to draw blood samples from the venous access point created by placing the infusion line. Therefore, the patient does not have to undergo multiple venous punctures to draw blood. This leads to less burden for the patient and reduces the risk of infections.

Benefits for study participants
The addition of the near infrared fluorescence imaging agent does not have direct benefits for the participating patients. Interference with standard clinical care is not expected since the surgeons and clinicians are to follow their normal standard of care.

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 equal to or older than 18 years;- Patients who are scheduled to undergo a pancreatectomy due to an insulinoma, another type of neuro-endocrine tumour or because of a suspected carcinoma.;- WHO performance score 0-2;- Signed informed consent

Exclusion criteria

- Breast feeding;- Pregnancy or the wish to become pregnant within 6 months;- Calculated creatinine clearance below 40ml/min;- Evidence of other malignancy in conventional imaging (suspicious liver, bone and lung lesions);- No informed consent

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	11
Type:	Anticipated

Ethics review

Approved WMO Date:	08-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2017-002831-41-NL
ClinicalTrials.gov	NCTnognietbekend
CCMO	NL62784.042.17