iPAVE - imaging Pituitary ActiVation by Exendin

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Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON52961

Source
ToetsingOnline

Brief title
iPAVE

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw,Diabetes Fonds

Intervention

Keyword: exendin, imaging, pituitary, type 2 diabetes

Outcome measures

Primary outcome

The main study parameter is the comparison of pituitary uptake of 68Ga-NODAGA-exendin in patients with and without adequate response (based on HbA1c or weight loss or classification by the treating diabetologist) to GLP-1R agonist treatment.

Secondary outcome

To assess the metabolic status of the patients by obtaining laboratory parameters, oral glucose tolerance testing, stimulated ACTH assay and urinary cortisol excretion tests

Study description

Background summary

68Ga-NODAGA-exendin PET/CT offers a unique opportunity to further elucidate the effects of GLP-1RA on the pituitary and to gain more insight into the mechanisms leading to GLP-1RA treatment failure. If we achieve positive results in this project, this would form the basis for a completely new research line aiming at defining the role the HPA axis plays in treatment of T2D. An improved understanding of the role of the HPA might also change our view of the development of obesity/metabolic syndrome and T2D and help to define new strategies for medical intervention, for example by specifically modulating the HPA axis.
It has been hypothesized that the improved outcome of combined GLP-1RA/glucagon/GIP treatment relay on the combination of positive dominant effects of the single compounds, thus overruling negative effects of the others. Such combined treatment regimens may proof efficient in patients with HPA oversensitivity, for example by lipolytic effects of glucagon counteracting the effects of HPA activation on adipose tissue.
Such results may change the treatment of obesity/T2D and would create new

possibilities for development of novel therapeutic strategies or novel drugs improving the health of the population. The outcomes of this project have the potential to boost innovation in diabetes/endocrinology research, which is of special importance in view of the ever-increasing rate of obesity and the associated morbidity and the subsequent healthcare costs, expected to rise to up to 40% of the annual healthcare budget in high prevalence countries.

Study objective

The study objective is to compare the pituitary uptake of 68Ga-NODAGA-exendin in patients with and without adequate response (based on HbA1c or weight loss or classification by the treating diabetologist) to GLP-1R agonist treatment, to increase understanding of the role of the HPA axis in T2D, which could contribute to the improvement of treatment strategies.

Study design

Subjects with T2D will be recruited from the outpatient clinic of the Department of Internal Medicine of the Radboud university medical center (Radboudumc) or through advertising (websites, social media). The subjects must have a minimum age of 18 years. After recruitment, subjects will visit the Department of Radiology and Nuclear Medicine in the Radboudumc in Nijmegen. After informed consent, metabolic characterization is perrformed that will consist of laboratory parameters and oral glucose tolerance testing. The second visit includes an ACTH assay and is performed after the stimulation with 10 microgram of GLP-1RA intravenously. Also, daily (unstimulated) cortisol excretion in 2 x 24h urine samples will be determined, these samples will be collected by the participant at home (creatinine excretion as internal control). All samples that are taken will be destroyed after analysis.
68Ga-NODAGA-exendin PET/CT scans will be performed in 10 patients with improved glycaemic control (decreased HbA1c of >=5 mmol/mol) or weight loss (>=5%) within one year of GLP-1RA treatment and in 10 patients without treatment response (as classified by the treating diabetologist). All patients will be injected with 100-150 MBq 68Ga-NODAGA-exendin, PET/CT scans will start with injection and dynamic image acquisition will be performed for one hour. One hour p.i., an additional static scan of the upper abdomen will be performed for determination of pancreatic uptake as measure for beta cell mass for reference to metabolic parameters/insulin production capacity. In 5 patients with high 68Ga-NODAGA-exendin uptake, an additional brain MRI will be performed for improved anatomical referencing.
Quantitative analysis of the scans will be performed for determination of binding capacity and absolute uptake in the pituitary and absolute uptake in the pancreas. Analysis of patient data (imaging, metabolic testing, cortisol production) will be performed and descriptive statistics will be obtained.
A fourth visit is required for 5 out of 20 patients, who will receive a MRI scan without contrast for anatomic correlation with the tracer uptake.

Study burden and risks

The patients will need to visit the Department of Radiology and Nuclear Medicine of the Radboudumc in Nijmegen 3 times in total. One visit is required for the stimulated ACTH assay, the second visit for the metabolic characterization (laboratory parameters and oral glucose tolerance testing) and during the third and last visit the PET/CT scan will be performed. All visits require an intravenous catheter, but will reduce the number of required venipunctures. Due to the placement of intravenous catheters, there is a small chance of bruising, pain and inflammation at the site of catheter placement.
The (unstimulated) cortisol excretion will be determined in 2 x 24h urine sample. The participant will need to collect these samples at home.
The PET/CT scan will be performed in 20 patients. In 5 patients with a high uptake in the pituitary gland, an additional MRI scan will be done (fourth visit). For the PET/CT scan, 100-150 MBq 68Ga-NODAGA-exendin-4 will be administered intravenously. High doses of Byetta® (exenatide) may result in nausea and headaches as has been reported in clinical trials studying the therapeutic effect of Byetta®. Nausea with a single event of vomiting has been observed in only 3 out of 103 cases in imaging studies after the administration of this radiopharmaceutical. In addition, single cases of low blood pressure and low blood glucose levels have been described after application of therapeutic or higher doses of Byetta®. Although low blood glucose levels only occurred after accidental heavy overdosing of Byetta®, patients will be closely monitored. In this study, we will administer 100 to 150 MBq 68Ga-NODAGA-exendin-4, corresponding to an exendin dose of 4 to 7 µg. Therefore, no (serious) adverse events will be expected. In case of administering 68Ga-NODAGA-exendin-4, the expected radiation exposure will be 0.023 mSv/MBq. In addition, 1.25 to 2 mSv will be received due to the low-dose CT. The total radiation exposure will be 3.6 to 5.5 mSv and is therefore considered minimal to little.
Despite the radiation exposure, 68Ga-exendin PET can be used to provide in vivo visualization and quantification of tissues expressing the GLP-1 receptor. This study will contribute to an improved understanding of the role of HPA axis in T2D treatment and can provide more insights regarding the mechanism leading to treatment failures in case of GLP-1 receptor agonist therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Inclusion criteria (patients with treatment response)
- Age >=18 years
- Subject is diagnosed with type 2 diabetes
- Subject showed response to GLP-1RA treatment (decrease in HbA1c >=5 mmol/mol and/or weight loss >=5%)
- Ability to sign informed consent, Inclusion criteria (patients without treatment response)
- Age >=18 years
- Subject is diagnosed with type 2 diabetes
- Subject showed no response to GLP-1RA treatment as classified by the treating diabetologist
- Ability to sign informed consent

Exclusion criteria

Exclusion criteria:
- Liver disease defined as aspartate aminotransferase or alanine aminotransferase level of more than three times the upper limit of the normal range
- Renal disease defined as MDRD <40 ml/min/1.73 m^2
- Pregnancy or the wish to become pregnant within 6 months after the study

- Breastfeeding
- Age <18 years
- Pituitary disorder
- Inability to sign informed consent
- Exclusion criteria for MR:
* Fragments, clips or devices in brain, eyes, spinal canal
* Implantable defibrillator or pacemaker (wires)
* Mandibular magnetic implants
* Neurostimulator, bladder stimulator, non-removable insulin pump
* Metal tissue-expander in chest
* Cochlear implant
* Ossicular replacement prosthesis

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-05-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	68Ga-NODAGA-[K40]-Exendin-4
Generic name:	68Ga-NODAGA-[K40]-Exendin-4

Ethics review

Approved WMO Date:	17-10-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-003566-13-NL
CCMO	NL67316.091.18