Effect of the GLP-1 receptor agonist exenatide on impaired awareness of hypoglycemia in type 1 diabetes

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Primary objective: to investigate the effect of treatment with the GLP-1ra exenatide on the awareness of and counterregulatory hormone responses to hypoglycemia in people with type 1 diabetes and impaired awareness of hypoglycemia. Secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON45806

Source
ToetsingOnline

Brief title
Exenatide and impaired awareness of hypoglycemia in T1DM

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes; Impaired Awareness of Hypoglycemia, hypoglycemia unawareness

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Astra-Zeneca

Intervention

Keyword: GLP-1 receptor agonist, hypoglycemia, impaired awareness of hypoglycemia, type 1 diabetes

Outcome measures

Primary outcome

Symptom score in response to the hyperinsulinemic hypoglycemic glucose clamp experiment

Secondary outcome

- Responses of counterregulatory hormones (adrenaline, glucagon, cortisol, growth hormone) to the hyperinsulinemic hypoglycemic glucose clamp
- Time until glycemic recovery from hypoglycemia after the hyperinsulinemic glucose clamp
- Maximal glucose excursion post-hypoglycemia after the hyperinsulinemic glucose clamp
- Time until glucose peak post-hypoglycemia after the hyperinsulinemic glucose clamp
- Area under the glucose concentration curve post-hypoglycemia after the hyperinsulinemic glucose clamp
- Amount of carbohydrates and total amount of calories consumed after hypoglycemia
- Number of severe hypoglycemic events during 6 weeks of treatment with exenatide or placebo
- Number of nocturnal hypoglycemic events during 6 weeks of treatment with exenatide or placebo

- Number of any hypoglycamic events during 6 weeks of treatment with exenatide or placebo

- Number of hypoglycemic events and time spent under hypoglycemic conditions as measured by continuous glucose sensor monitoring

- Glucose variability as measured by continuous glucose sensor monitoring

- Vital signs during the hyperinsulinemic hypoglycemic glucose clamp

- Gastrointestinal adverse effects during 6 weeks of treatment with exenatide or placebo

Study description

Background summary

Iatrogenic hypoglycemia is the most frequent, acute, complication of insulin therapy in people with type 1 diabetes. These patients experience on average 2-3 hypoglycemic events per week and one severe event requiring external assistance every year. Accurate and timely recognition of the typical symptoms of falling glucose levels are of pivotal importance to prevent severe hypoglycemia. However, 25-40% of patients with type 1 diabetes have lost the capacity to timely detect hypoglycemia, a condition referred to as impaired awareness of hypoglycemia (IAH) that specifically increases the risk for severe, potentially hazardous, hypoglycemia up to sixfold. IAH is usually the end-result of a process of habituation to recurrent hypoglycemia and meticulous avoidance of hypoglycemia for 2-3 weeks can reverse this process, thus ameliorating symptomatic awareness of hypoglycemia. However, the often coexistent worsening of glycaemic control precludes such an approach as a viable treatment option.
Many patients with IAH suffer from high glucose variability, in which both hypoglycemic events and hyperglycemic excursions occur at high frequency. Indeed, hyperglycemic excursions often develop after recovery from hypoglycemia, usually because of ingesting (too many) carbohydrates in the context of hyperglucagonemia. In turn, correction of such a hyperglycemic excursion too aggressively, especially in the context of failing counterregulatory hormone responses and impaired awareness, creates a high risk for hypoglycemia.
More stability in day-to-day glucose control with reduced hypoglycemic exposure may be important to resolve IAH. Paradoxically however, improvement in

awareness of hypoglycemia may also stimulate hyperglycemic excursions after hypoglycemia, because the stronger hunger response (as a component of improved awareness) may enhance the ingestion of carbohydrates, thus worsening overall glycaemic control. Glucagon-like-peptide-1 receptor agonists (GLP-1RAs), developed for the treatment of type 2 diabetes, may reduce glucose variability, because these agents reduce postprandial glucose excursions without increasing the risk of hypoglycemia. These agents also reduce body weight, because they delay gastric emptying, cause early satiety and reduce food intake. Recently, treatment with GLP-1RAs in people with type 1 diabetes improved postprandial and overall glucose control and reduced insulin requirements and glucose variability. These agents have not been tested in patients with type 1 diabetes and IAH. We posit that treatment with GLP-1ra (added to insulin therapy) will reduce glucose variability and the incidence of hypoglycemia, so that IAH can be improved. Moreover, since such treatment will limit food intake in the recovery period after hypoglycemia, we posit that overall glycemic control will not deteriorate.

Study objective

Primary objective: to investigate the effect of treatment with the GLP-1ra exenatide on the awareness of and counterregulatory hormone responses to hypoglycemia in people with type 1 diabetes and impaired awareness of hypoglycemia.

Secondary objective: to investigate the effect of treatment with the GLP-1ra exenatide on the glycemic recovery from hypoglycemia and the post-hypoglycemic glucose excursion in people with type 1 diabetes and impaired awareness of hypoglycemia.

Study design

Randomized double-blind placebo-controlled cross-over trial
2 periods of 6 weeks treatment with exenatide versus placebo
5 days blinded continuous glucose sensor monitoring in final week of each treatment period
Hyperinsulinemic hypoglycemic glucose clamp at the end of each treatment period to quantitate symptomatic awareness of hypoglycemia

Intervention

6 weeks treatment with the glucagon-like peptide receptor agonist exenatide or placebo according to the following regimen:
weeks 1-2: exenatide BID 5 microgram sc
weeks 3-6: exenatide BID 10 microgram sc

Study burden and risks

The extent of the burden of participating to this study include the following:
- Total time spent: 16 weeks: 2 periods of 6 weeks and a 'wash-out' of 4 weeks. Prior to randomization, participants will visit the clinic for a screening examination. During both treatment periods, two telephone visits and one regular visit (for inserting the glucose sensor) will be scheduled.
- During treatment periods: subcutaneous injection of study medication (exenatide or placebo) twice daily. A special designed injection pen, comparable to conventional insulin pens, is used for these injections.
- Final week of treatment periods: continuous glucose sensor measurement for 5 days
- Final day of treatment periods: 5-hour experiment involving hyperinsulinemic hypoglycemic glucose clamp (8AM-1PM). This experiment involves stepwise lowering of plasma glucose levels to 2.5 mol/l with intravenous infusions of insulin and glucose 20% according to a titration protocol. Hypoglycemia normally elicits typical symptoms, including sweating, feeling hungry, palpitations, trembling and tingling, and - to a lesser extent - concentration disturbances, tiredness, difficulty speaking and visual disturbances. Such hypoglycaemia does not cause severe cognitive dysfunction, coma or epileptic insults. This hypoglycemic phase does not last longer than 45 minutes. The recruited patients' condition of impaired awareness means that they will probably remain largely unaware of these typical symptoms, although we hypothesize that exenatide may enhance these symptoms.

Potential risks and adverse events associated with participation:
1. during the 6-week treatment periods:
- Nausea and vomiting. These are well-known adverse effects associated with the use of GLP-1 receptor agonists that may affect up to 20% of patients, but much less when lower starting doses are used.
- Hypoglycaemia. The risk of hypoglycaemia may be increased when exenatide is started as prior studies have shown that insulin requirements decrease; to mitigate this risk, the dose of insulin will be decreased by 20% in the first week of each treatment period and further adjusted on the basis of frequent glucose self-measurements.
- Hyperglycaemia. This is a risk largely associated to diabetes itself, but could potentially increase in the placebo treatment arm as a consequence of the 20% lowering of insulin (see above).
- Local skin reactions or inflammation. This can be a consequence of subcutaneous injection per se or (local) allergy, the risks of which are low.
- Rare adverse reactions: anafylactic reactions and acute pancreatitis
2. Continuous glucose sensor monitoring:
- Local skin reactions or inflammation. This can be a consequence of subcutaneous insertion of the sensor, but this risk is very low.
3. Hyperinsulinemic hypoglycaemic glucose clamp
- Symptoms of hypoglycemia. These are anticipated as per protocol (see above)
- Deeper hypoglycemia than targeted. This risk is minimal because of the simultaneous infusion of glucose and glucose measurements every 5 minutes.
- Hematoma as a result of venous cannulations

- Flebitis as a consequence of glucose 20% infusion. This occurs occasionally but is usually self-limiting
- Disruption in glycemic control after the experiment. Glucose levels may show more fluctuations, but this is usually transient and can be mitigated by intensifying glucose self control.

It is essential for patients with type 1 diabetes that they retain the capacity to timely and accurately detect hypoglycemia. Patients who will be recruited to this study have lost this capacity and are consequently at high risk of developing severe hypoglycemia. In this project, it will be investigated whether this loss of hypoglycemic awareness can be treatment with exenatide. In this light, we believe that the burden of 16 weeks of experimental treatment and the two experimental days involving hypoglycemic glucose clamps are reasonable.

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

* Type 1 diabetes, disease duration >1 year
* Age >18 years, * Insulin treatment according to basal-bolus insulin regimen (injections or insulin pump)
* Impaired awareness of hypoglycemia as assessed by a score of 3 or more on the modified Dutch translation of the Clarke questionnaire
* Glycated haemoglobin (HbA1c) *42 mmol/mol (6%) and *75 mmol/mol (9.0%)
* Ability to provide informed consent

Exclusion criteria

* Treatment with incretin-based therapy (DPP-IV inhibitors or GLP-1RAs)
* Known intolerance to GLP-1RAs (including allergy)
* Treatment with glucose-modefying or immune-modefying agents, e.g. prednisolon
* History of cardiovascular disease (e.g. myocardial infarction, stroke, heart failure) or laser coagulation for proliferative retinopathy (past 6 months)
* Proliferative retinopathy
* Symptomatic diabetic neuropathy
* Diabetic nephropathy as reflected by albumin-creatinin ratio >30 mmol/mg or MDRD <60 ml/min/1.73 m2
* History of pancreatitis (acute or chronic) or pancreatic cancer
* Body-mass index <19 or >40 kg/m2
* Blood pressure >160/90 mmHg
* Use of premixed insulin or of long-acting insulin alone
* Total daily insulin dose requirements <20 units unless on pump treatment
* Pregnancy or unwillingness to undertake measures for birth control

Study design

Design

Study phase:	2
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):	21-02-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Byetta
Generic name:	Exenatide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Novorapid
Generic name:	Aspart insulin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-09-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-11-2017
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	EUCTR2016-000790-21-NL
ClinicalTrials.gov	NCT02735031
CCMO	NL56979.091.16

Study results

Date completed:	01-03-2018
Actual enrolment:	13