The effect of the secondary bile acid glycodeoxycholic acid as a therapy for diabetes.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20316

Source
Nationaal Trial Register

Brief title
TRADE

Health condition

type 2 diabetes mellitus

Sponsors and support

Primary sponsor: Academic Medical Center (AMC), Amsterdam, The Nettherlands
Source(s) of monetary or material Support: ZonMw en Diabetes Fonds

Intervention

Outcome measures

Primary outcome

Secretion of GLP-1 and insulin, postprandial inflammation and postprandial hyperlipidemia. THe primary objective of phase 1 is to determine safety of long-term gDCA administration in healthy volunteers.

Secondary outcome

The effect of gDCA administration on bile acid metabolism, glucoregulatory and gut hormones, resting energy expenditure, microbiome, appetite and satiety, cholesterol elimination.

Study description

Background summary

SUMMARY

Rationale: Bile acids (BAs) and their receptors (e.g. TGR5, Takeda G-coupled protein 5 and VDR, vitamin D receptor) have gained interest in development of treatment modalities for type 2 diabetes mellitus (T2D). Postprandial hyperglycemia, inflammation and hyperlipidemia are important risk factors for cardiovascular disease. Preliminary data show that postprandial portal secondary BAs have high affinity for TGR5 /VDR with important consequences for Glucagon like peptide - 1 (GLP-1) secretion and inflammation respectively. Also, BAs may promote cholesterol elimination via the ATP binding cassette (ABC) half transporters G5 and G8 (ABCG5/G8).In this study, we want to investigate if the secondary BA glycodeoxycholic acid (gDCA) increase GLP-1 secretion, reduce inflammation and hyperlipidemia after a meal.

Objective: To study the effects of gDCA on postprandial GLP-1 secretion, inflammation responses and hyperlipidemia in healthy lean male subjects and male T2D patients. The secondary objectives are to evaluate the effect of gDCA and ezetimibe on cholesterol elimination assessed as total faecal sterol concentration and plasma lipid profile/composition and the effect of different formulations on the gDCA bioavailability.

The study consists of three phases:

Phase 1: Safety study in healthy volunteers (N=20). Subjects will be randomized to 30 days gDCA or 30 days enteric coated gDCA.

Phase 2: Male patients with type 2 diabetes mellitus (T2D) (N=10) receiving 30 days (enteric coated) gDCA.

Phase 3: Male patients with T2D receiving 30 day (enteric coated) gDCA (N=10) in combination with ezetimibe.

Intervention: Subjects will be treated with 10 mg/kg/day gDCA or 10 mg/kg/day enteric-coated gDCA for 30 days. In phase 3, subjects will receive ezetimibe 20 mg per day on top of the gDCA supplementation. In addition, subjects will undergo 3 mixed meal tests (MMTs). The mixed meal test will be performed using Nutridrink compact (Nutricia, Zoetermeer, the Netherlands), a commercial liquid meal containing a mix of essential macronutrients. Before and after the MMT, energy expenditure (EE) is measured by indirect calorimetry and 24 hour stools + morning stool sample will be collected to investigate changes in the microbiome and the faecal sterol concentration. We will ask participants to fill in online or written dietary diary for 3 days prior to the MMTs to ensure the stability and similarity of the gut microbiota during the study period. After each MMT, appetite will be measured by the Universal Eating scale. Body composition will be measured each study visit using whole-body air displacement plethysmography (BODPOD).

Study objective

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Study design

3 mixed meal tests at Day 0, Day 15 and Day 31.
Timepoints: 0, 15,30,45,60,90,120,150,180,240 and 300 minutes after ingestion of the mixed meal.

Intervention

In phase 1, the healthy subjects will be randomized into 2 groups. The first group (N=10) will receive 10 mg/kg/day gDCA for 30 days, the other group (N=10) will receive 10 mg/kg/day enteric coated gDCA for 30 days. The first 5 healthy subjects will be included in the treatment arm giving normal/regular gDCA. When no SAEs occur, the next step will be to include 5 healthy subjects in the arm giving enteric coated gDCA. When no SAEs occur the last 10

subjects will be assigned according to a predefined scheme. At the phase 2 we include 10 T2D male patients. The 10 T2D patients will receive gDCA or enteric coated gDCA. The dosage and which form of gDCA (normal or enteric coated) will be based on the results of the pilot study (phase 1) regarding safety. In the third (final) phase we want to include10 T2D male patients. The 10 T2D patients receive (enteric coated) gDCA (depending on phase 1) and 20 mg ezetimibe per day for 30 days.

Step down procedure
We will perform liver function tests (ALAT, ASAT, AF, GGT and bilirubin) in subjects after 1 week of gDCA administration (4 mL heparin plasma), during the second and the third MMT. When liver function tests rise during the administration of (enteric coated) gDCA between 2 and 4 times upper reference limit, we lower the daily dosage of the (enteric coated) gDCA to 5 mg/kg/day. Additionally, we intensify the monitoring of liver function to 2 times per week during administration until they return to normal concentrations. When liver functions tests reach the concentrations of 4 times upper reference limit, the gDCA administration will be stopped and the study ends.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

•Ability to provide informed consent

•Age: 18 years or older at the time of signing the informed consent

Specific inclusion criteria for the healthy lean subjects group:

•BMI 18,5 – 25 kg/m2 or a BMI between 25 and 30 kg/m2 and waist circumference between 79 cm and 94 cm.

•HOMA-IR index: ≤ 2.0 (measured as fasting insulin (pmol/L) x fasting glucose (mmol/L)) / 135)

Specific inclusion criteria for the T2D patients group:

•Stable T2D treated with diet and/or medication only (medication not changed in the past 3 months)

•HbA1c 53-64 mmol/mol

•BMI > 25 kg/m2

Exclusion criteria

•Use of medication that interferes with BA metabolism (colesevelam, colestimide, ursodeoxycholic acid).

•Diabetes treatment with dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists or insulin

•Hypercholesterolemia treatment with statins or fibrates unless on a stable dose for at least 3 months prior to screening

•Use of nicotinic acid or derivates of nicotinic acid within 4 weeks prior to screening

•Presence of contra indications for the use of ezetimibe (see SPC)

•Use of other medication such as the following: vitamin K antagonists, ciclosporine, antacids containing aluminium hydroxide or aluminium oxide

•Cholecystectomy

•Gastro-intestinal disorders, including gallstone disease

•Nefropathy checked by blood chemistry (creatinine, eGFR)

•Liver disease checked by blood chemistry (ASAT, ALAT, GGT, AF, bilirubin)

•Weight increase or decrease >10% in previous 3 months

•Alcohol use >3 units/day

•Tobacco use

•XTC, cannabis, cocaine or opioids abuse

•Likely to leave the study before its completion

•Participation in other intervention studies 3 months before or after the duration of this study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	18-06-2018
Enrollment:	40
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion Date:	26-09-2017
Application type:	First submission

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
NTR-new	NL6526
NTR-old	NTR6714
Other	NL.61855.018.17 : METC2017_133

Study results