The Effect of UrsodeoXyCholicacid (UDCA) and ezetimibe on total faecal steRol ExcreTion and plasma lipid lEvels

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The primary objective is to evaluate the effect of UDCA and ezetimibe on cholesterol elimination assessed as total faecal sterol concentration. Secondary objective is to assess the effect of UDCA and ezetimibe on plasma lipid profile/composition.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary disorders congenital
Study type	Interventional

Summary

ID

NL-OMON47926

Source
ToetsingOnline

Brief title
EXCRETE

Condition

- Hepatobiliary disorders congenital
- Lipid metabolism disorders

Synonym
Familial hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum (AMC)
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cardiovascular risk, Ezetimibe, Familial hypercholesterolemia, UDCA

Outcome measures

Primary outcome

Main endpoint is the total faecal sterol concentration (faecal neutral sterol concentration (FNS) + faecal bile acid concentration).

Secondary outcome

Secondary endpoint is plasma lipid profile/composition: LDL-c, HDL-c, TG, apoB, apoA1.

Study description

Background summary

Atherosclerosis is the main underlying cause of cardiovascular disease (CVD). Increasing cholesterol elimination is a widely used strategy to reduce CVD. Intestinal cholesterol secretion is mediated via the ATP binding cassette (ABC) half transporters G5 and G8 (ABCG5/G8) while cholesterol absorption is mediated by the Niemann-Pick C1 Like (NPC1L1) protein, which is inhibited by ezetimibe. There is growing evidence that hydrophilic bile acids like ursochol (ursodeoxycholic acid, UDCA) promote ABCG5/G8 activity in mice. We hypothesize that UDCA on top of ezetimibe leads to an increased cholesterol excretion via the feces by stimulating ABCG5/8 and preventing absorption of cholesterol due to blocking NPC1L1 and therefore promoting elimination of cholesterol from the body.

Study objective

The primary objective is to evaluate the effect of UDCA and ezetimibe on cholesterol elimination assessed as total faecal sterol concentration. Secondary objective is to assess the effect of UDCA and ezetimibe on plasma lipid profile/composition.

Study design

The current study is an investigator initiated, single-centre, randomized,

double blind, placebo-controlled , cross-over, proof of concept study, to explore the translational relevance of UDCA on top of ezetimibe on cholesterol elimination.

Intervention

One group will receive UDCA 600 mg orally once a day, the other group will receive a matching placebo. This will be on the background of 20 mg/day ezetimibe.

Study burden and risks

There will be five study visits with a questionnaire and physical examination. Also, there will be five times blood sampling with a total amount of blood of 60 ml. In addition, they are subjected to behavioral changes, such as a dietary registration, ingestion of D4-sitostanol and the collection of 5 fecal stool samples of 5 mg per sample. D4-sitostanol does not confer any health risks.
UDCA is a registered medicinal product for a number of indications and considered safe. Most prevalent side effect of UDCA is diarrhea, a risk of 1-10% exists for this. Ezetimibe is a registered medicinal product for hypercholesterolemia and considered safe. Most important side effect of ezetimibe is elevated liver enzymes and rhabdomyolysis, most prevalent when given in combination with statin therapy. The risk of developing these adverse events is considered to be very low in our study population (0.1% - 1%)

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

Hypercholesterolemia
Aged 18 years or older
LDL > 2.6 mmol/L

Exclusion criteria

* Medical, surgical, laboratory or other conditions, which in the judgment of the Physician Investigator would make the subject unsuitable for enrollment, or potentially interfere with subject participation or completion of the study, * Suffering from an inflammatory bowel disease, e.g. Crohn*s disease or ulcerative colitis., * Suffering from gall stones or another biliary disease., * Suffering diabetes mellitus (type I or II)., * Recent history of, or current drug or alcohol abuse, * AST or ALT levels > 2 x ULN, * Unable or unwilling to comply with the protocol requirements or deemed by the investigator to be unfit for the study., * Presence of contra indications for the use of UDCA and ezetimibe (see SPC), * Use of lipid lowering drugs such as the following:, o Statins and fibrates unless on a stable dose for at least 3 months prior to screening, o Use of nicotinic acid or derivates of nicotinic acid within 4 weeks prior to screening, o Use of cholestyramine or colestipol, * Use of other drugs such as the following:, o Ciclosporine, o Antacids containing aluminium hydroxide or aluminium oxide, * Likely to leave the study before its completion

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-09-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ezetrol
Generic name:	Ezetimibe
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	UDCA
Generic name:	Ursodeoxycholic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 19907
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-003281-84-NL
CCMO	NL56321.018.16
OMON	NL-OMON19907