The Role of microbial produced ethanol in etiology of non-alcoholic steatohepatitis

Gepubliceerd: 22-04-2019 Laatst bijgewerkt: 13-12-2022

We hypothesize that subjects with NASH produce more ethanol after a mixed meal tolerance test than subjects with a healthy liver after receiving a infusion with fomepizole.

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20655

Bron
NTR

Verkorte titel
ETHANASH trial

Aandoening

NASH

Ondersteuning

Primaire sponsor: Amsterdam UMC, locatie AMC
Overige ondersteuning: Amsterdam UMC, locatie AMC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To investigate whether microbial produced ethanol plays a role in the development of NASH.

Toelichting onderzoek

Achtergrond van het onderzoek

Changes in the composition of the gut microbiota have been associated with alterations in host metabolism and recent evidence suggest that gut microbiota might also be involved in the development of Non-Alcoholic Fatty Liver Disease (NAFLD) and subsequent Non-alcoholic steatohepatitis (NASH). So far, however, causality has not been demonstrated. Among many gut microbial metabolites, endogenous intestinally produced ethanol has gained interest in the past decade for its involvement in the development of NAFLD. Ethanol is produced by intestinal bacteria has been suggested that ethanol might play a role in the development of NAFLD, especially in the transition from NAFLD to NASH. When produced in significant amounts, hepatic ethanol metabolism inhibits beta-oxidation of fatty acids which will induce storage of lipids in the liver. Endogenously produced ethanol reaches the liver via the portal vein and is then rapidly removed from the circulation via extremely efficient hepatic mechanisms, leaving almost untraceable concentrations in the peripheral plasma if liver function is uncompromised. Several studies have however showed that subjects with NASH (known to have a compromised liver function) have increased peripheral concentrations of ethanol, however these concentrations are so low that one might argue whether this is clinical relevant regarding the development of NASH. The first step in ethanol catabolism is the oxidation of ethanol to acetaldehyde using NAD+, mainly via the hepatic enzyme alcohol dehydrogenase. Fomepizole (4-methylpyrazole) is a specific inhibitor of the enzyme alcohol dehydrogenase. In a previous study, a significant elevation of peripheral plasma ethanol concentrations were observed in lean subjects who were treated with fomepizole after intake of lingonberry juice. Since subjects with NASH might have more ethanol producing bacteria, we anticipate to find increased concentrations of ethanol in subjects with NASH compared to healthy control subjects during a mixed meal test after the infusion of fomepizole. Moreover, when intestinal microbiota is temporarily eradicated by a short term oral antibiotic course, we expect to see no increase in peripheral plasma ethanol levels upon fomepizole infusion in patients with NASH.

Doel van het onderzoek

We hypothesize that subjects with NASH produce more ethanol after a mixed meal tolerance test than subjects with a healthy liver after receiving a infusion with fomepizole.

Onderzoeksopzet

baseline, visit 1, visit 2

Onderzoeksproduct en/of interventie

Subjects will undergo an ultrasonography of the liver to assess hepatic steatosis and will undergo a clinical mixed meal tolerance test and get an infusion with fomepizole or saline (placebo). Only NASH patients will also receive oral antibiotics course of 7 days followed by

mixed meal test with fomepizole infusion.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Diagnosis of NASH on liver biopsy taken on clinical grounds at the outpatient clinic, or healthy volunteer
- 18-65 years of age
- BMI > 25 kg/m2
- Subjects should be able to give informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Primary lipid disorder
- Known genetic basis for insulin resistance or glucose intolerance
- Ethanol intake > 2 U/week
- Pregnancy, females who are breastfeeding
- Hepatitis B and/or C
- Liver cirrhosis
- Auto-immune hepatitis

- Wilson disease3/ alpha 1-antitripsine deficiency
- Hemochromatosis
- Use of drugs interacting with fomepizole (products requiring CYP2E1 for metabolizing).

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm

Controle: N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	22-04-2019
Aantal proefpersonen:	20
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Toelichting
We will not share IPD

Ethische beoordeling

Positief advies

Datum:	22-04-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7693
Ander register	NA : METC Amsterdam UMC, lokatie AMC 2018_331

Resultaten