Effect of Transjugular Intrahepatic Portosystemic Shunt on pharmacokinetics

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We hypothesize that TIPS placement has an significant effect on drug metabolism and bile acid metabolism.

Ethische beoordeling	Positief advies
Status	Anders
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24097

Bron
NTR

Verkorte titel
TIPS and PK

Aandoening

Cirrhosis, portal hypertension.
Levercirrose, portale hypertensie.

Ondersteuning

Primaire sponsor: Academic Medical Center (AMC), Amsterdam
Overige ondersteuning: Academic Medical Center (AMC), Amsterdam

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. To assess the effect of TIPS placement on drug metabolism of different drugs, metabolized by different metabolic pathways in patients with cirrhosis using the drug cocktail approach after oral administration. Drug exposure is quantified by assessment of the area under the plasma concentration versus time curve (AUC) for each drug.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Liver cirrhosis is the end stage of chronic liver injury, and is associated with portal hypertension and a decreased function of the liver. Drug dosage in patients with cirrhosis is difficult due to this decreased function. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a highly effective intervention to reduce elevated portal pressure and reduce complication rates of portal hypertension. Hepatic biotransformation of endogenous toxins, hormones or the pharmacokinetics of drugs and bile acid metabolism may be affected by TIPS placement, but prospective controlled studies are lacking.

Objective: To assess the effect of TIPS on drug metabolism of different drugs, metabolized by different metabolic pathways in patients with an elective TIPS placement using a cocktail approach, and to assess the effect of TIPS on bile acid metabolism.

Doel van het onderzoek

We hypothesize that TIPS placement has an significant effect on drug metabolism and bile acid metabolism.

Onderzoeksopzet

Drug cocktail administration and measurement will take place two weeks before TIPS placement, a day after TIPS placement and twelve weeks after TIPS placement.

PK samples will be collected at approximately t=0, t=0,5, t=1, t=1.5, t=2, t=3, t=4, t=6, t=9 hours, 24 hours
(day 1) and 72 hours (day 3) after drug cocktail administration.

Onderzoeksproduct en/of interventie

This study consists of three interventions per patient. Patients will receive a single oral administration of a drug cocktail two weeks before TIPS placement, a day after
TIPS placement, and twelve weeks after TIPS placement. The oral drug cocktail consists of 50 mg caffeine, 5 mg warfarin, 20 mg omeprazole, 20 mg metoprolol and 0.015 mg/kg midazolam. In addition to the drug cocktail, patients undergo a mixed meal tests (MMT),

using Nutridrink compact, and measurement of body expenditure and body composition.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Liver cirrhosis as documented by liver biopsy or
elastography (e.g. Fibroscan > 15 kPa) in combination with usual radiological and biochemical signs.

- Age > 18 years.

- Elective indication for TIPS (recurrent tense ascites, recurrent/refractory hepatic hydrothorax, or (recurrent) oesophageal or gastric bleeding treated with endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) more than 2 weeks prior to screening.

- Signed informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Age > 75 years.

- History of grade III or IV HE or chronic overt HE.

- Patients with (recurrent) oesophageal or gastric bleeding treated with endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) within 2 weeks previous to screening.

- Patients who meet the criteria for emergency TIPS for uncontrolled bleeding.

- Spontaneous Bacterial Peritonitis (SBP) during the past 7 days.

- Child Pugh score ≥ 10.

- MELD score > 20.

- Serum bilirubin 51 > µmol/L.

- INR > 1.7.

- Serum creatinine > 185 µmol/L.

- Complete portal vein thrombosis.

- Hepatocellular Carcinoma

- Polycystic liver disease/ multiple large liver cysts.

- Concomitant active infection.

- Congestive heart failure.

- Pulmonary hypertension

- Bile duct obstruction with dilatation of the bile ducts.

- Overt neurologic diseases such as Alzheimer’s disease, Parkinson’s disease.

- Pregnant or breastfeeding women.

- Drug abuse or alcoholism (>3 units of alcohol per day).

- Use of alcohol for at least 3 days prior to each study day.

- Strenuous exercise for at least 3 days prior to each study day, defined as more than 1 hour of exercise per day.

- Use of prescription or non-prescription drugs and herbal or dietary supplements within 14 days prior to the first administration of the drug cocktail, that will not be taken after TIPS placement.
- Use of tobacco products (induction liver enzymes).

- Drinking of coffee/thee or caffeine containing beverages (caffeine) within 1 day prior to study (based on the half-life of caffeine: t1/2=5 hours).

- Eating/drinking of grapefruit and grapefruit-containing products or star fruit for at least 2 days prior to each study day.

- Allergy for the study medications

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Anders
(Verwachte) startdatum:	04-07-2018
Aantal proefpersonen:	11
Type:	Onbekend

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	08-01-2019

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	NL7465
NTR-old	NTR7707
Ander register	MEC AMC : 2018_089

Resultaten