Transjugular intrahepatic portosystemic shunt (TIPS): effect on pharmacokinetics

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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.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON48883

Source
ToetsingOnline

Brief title
Effect of TIPS on pharmacokinetics

Condition

- Hepatic and hepatobiliary disorders

Synonym
Cirrhosis, scarring of the liver

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cocktail, CYP450, Pharmacokinetics, Transjugular Intrahepatic Portosystemic Shunt

Outcome measures

Primary outcome

Primary study endpoint is the difference in area under the plasma concentration versus time curve for each drug following the oral administration of the drug cocktail two weeks before TIPS placement, a day after TIPS placement, and twelve weeks after TIPS placement.

Secondary outcome

Secondary endpoints include the difference in the following pharmacokinetics parameters: clearance, volume of distribution, absorption rate, mean residence time and elimination half-life. In addition, we want to assess the effect of TIPS placement on the postprandial levels of bile acids, glucose, insulin, c-peptide, GLP-1, FGF19, C4 and glucagon by MMT.

Study description

Background summary

Liver cirrhosis is the end stage of chronic liver injury, and is associated with portal hypertension. 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 may be affected by TIPS placement, but prospective controlled studies are lacking.

Study 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.

Study design

Open-label, single-dose crossover intervention study.

Intervention

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.

Study burden and risks

Additionally to an admission for elective TIPS placement and observation (standard of care), patients will undergo a screening visit, and two additional 10-hour hospital admissions for administration of the oral drug cocktail, MMT and subsequent blood sampling. The second administration will take place during the (standard of care) observation after TIPS placement.
Patients will visit the clinic two times (day 1 and 3) after each oral administration for PK analysis and coagulation monitoring. One urine sample will be taken to perform an urinary drug screening and for analysis of sodium and potassium levels. A total of 64 blood samples will be drawn. During screening visit this consists of 4 samples for monitoring of laboratory parameters (n=3) and for pharmacogenetic analysis of liver enzymes (n=1). During each admission for administration of the cocktail 20 samples will be drawn for PK and metabolic analysis (bile acids and other postprandial markers) via an intravenous catheter. A total volume of 306 mL blood will be obtained for this study. Effects of TIPS placement on energy metabolism will be assessed with indirect calorimetry and body composition.

This study will generate information regarding alterations in pharmacokinetics due to TIPS and bile acid metabolism before and after TIPS placement and may therefore be of future benefit for patients who undergo TIPS placement using medication.

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

1. Liver cirrhosis as documented by liver biopsy or elastography (e.g. Fibroscan > 15 kPa) in combination with usual radiological and biochemical signs.
2. Age > 18 years.
3. 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.
4. Signed informed consent

Exclusion criteria

Absolute contraindications for TIPS placement
Child-Pugh score >= 10
MELD score > 20

Serum bilirubin 51 > µmol/L
INR > 1.7
Serum creatinine > 185 µmol/L
Active drug abuse or alcoholism
Overt neurologic disease

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-06-2019
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO Date:	04-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2019
Application type:	Amendment

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

No registrations found.

In other registers

Register	ID
CCMO	NL65505.018.18