Effect of bile drainage and rifampicin, a pregnane X receptor agonist, on clinical and biochemical recovery of patients with obstructive cholestasis

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To study the effect of alleviation of obstructive cholestasis by biliary drainage with or without rifampicin on serum bilirubin levels, quality of life, itch intensity, and serum and/or biliary bile salt, ATX, LPA, FGF-19 and biliary HCO3- levels in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON36732

Source
ToetsingOnline

Brief title
BIDRIP trial

Condition

- Hepatic and hepatobiliary disorders

Synonym
obstructive cholestasis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: This work was supported by a grant □Primary sclerosing cholangitis□ from the □Deutsche Crohn and Colitis Vereinigung□

Intervention

Keyword: Obstructive Cholestasis, Pruritus, Rifampicin

Outcome measures

Primary outcome

Serum bilirubin levels

Secondary outcome

• Quality of life (QoL; SF-36) and itch intensity (VAS),

• Serum: bilesalt profil, lysofosfaticid acid, autotaxine, fribroblast growth

factor 19, Asat, Alat, alkaline phosphatase and gamma-glutamyltransferase

• Bile: lysofosfaticid acid, autotaxine, fribroblast growth factor 19 and

bicarbonate

Study description

Background summary

The antibiotic rifampicin is identified as an activator of the nuclear receptor pregnane X receptor (PXR). In vitro and in vivo studies have shown that rifampicin, by being a PXR-ligand, has several possible pharmacological targets for the treatment of cholestasis and thereby improves liver cell secretion and cholestasis-induced pruritus. In a pilot study eight patients with progressive hepatocellular secretory failure (serum bilirubin >255µmol/L) were successfully treated with rifampicin, resulting in amelioration of bilirubin levels, and pruritus also improved rapidly (article under submission). Rifampicin is effective in cholestasis associated pruritus. It is shown that short-term treatment with PXR agonists such as rifampicin is highly effective and safe. Rifampicin for short duration, not longer than two weeks, is associated with a low risk of hepatotoxicity, Rifampicin-induced hepatitis is only seen after 2-3 months of treatment.
Various cholestatic disorders are associated with pruritus. Recent results of our group suggest that lysophosphatidic acid (LPA) and autotaxin (ATX) play a

critical role in cholestatic pruritus. However, the source of increased serum ATX levels remains to be elucidated. Certain substances in bile may induce gene expression of autotaxin. It is our aim to reveal the nature of these substances. Without adequate therapy chronic cholestatic diseases can progress through stages of inflammation and fibrosis to cirrhosis. The function of bile salts during cholestasis is ambiguous: they act as pro-inflammatory agents on the one hand and as signaling ligands via membrane bound and nuclear receptors on the other hand. It is not known how hepatocytes and cholangiocytes gain resistance against these noxious compounds in bile. Our group hypothesized an import role for HCO3- secretion in the biliary tract as a defense mechanism against noxious compounds in bile.

Study objective

To study the effect of alleviation of obstructive cholestasis by biliary drainage with or without rifampicin on serum bilirubin levels, quality of life, itch intensity, and serum and/or biliary bile salt, ATX, LPA, FGF-19 and biliary HCO3- levels in patients routinely undergoing biliary drainage via the percutaneous or endoscopic route. Itch intensity will be quantified before and during drainage with visual analogue scales (VAS).

Study design

Interventional study with invasive measurements

Intervention

Rifampicin 150 mg twice a day for seven days and blood samples (3x 15 ml)

Study burden and risks

Patients who are admitted for PTC or ERC regularly stay for at least 24 hours and are seen again in the outpatient clinic one week later. Blood sampling will be performed at the day of PTC/ERCP, after 24 hours and after one and four weeks. Six bile samples will be collected from the biliary drain in the first 24 hours and one sample a week later. The risks of the study are related to the blood sampling; hematoma and phlebitis and side-effects of the use of Rifampicin as described in the *Farmacotherapeutisch Kompas*: nausea, vomiting, epigatrsic pain, elevated liver enzymes, jaundice, itch, headache and dizziness. Rifampicin for short duration is associated with a low risk of hepatotoxicity, rifampicin-induced hepatitis is only seen after 2-3 months of treatment.

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

- Male or female with severe obstructive cholestasis for whom biliary drainage by PTC or nasobiliary drainage by ERCP is clinically indicated.
- An established diagnosis of obstructive cholestasis by ultrasound-scan (US-scan), magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic retrograde cholangiopancreatography (ERCP).
- Age 18-90 years
- Able to understand and give fully informed written consent
- Hyperbilirubinemia > 170 umol/L
- Cholestatic serum enzyme pattern

Exclusion criteria

- Patients with purely hepatocellular, non-obstructive cholestasis in whom biliary drainage by PTC or ERCP is not clinically indicated
- Patients with known allergy to rifampicin

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-10-2012
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rifampicin
Generic name:	Rifampicin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	06-12-2011
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: 24804
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-001549-34-NL
CCMO	NL34567.018.11
OMON	NL-OMON24804