Pharmacokinetics of UDCA in serum and bile in patients with early stage PBC (stage I-III) and in healthy volunteers

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To assess the bile acid composition of cystic bile and serum pharmacokinetics after a 3-week treatment with UDCA and to correlate pharmacokinetic parameter sof UDCA in bile and serum during steady state.To compare the composition of bile acids and...

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

Summary

ID

NL-OMON31024

Source
ToetsingOnline

Brief title
URT-14/BIO

Condition

- Hepatic and hepatobiliary disorders

Synonym
early stage primary biliary cirrhosis, PBC

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Falk Pharma GmbH
Source(s) of monetary or material Support: Dr. Falk Pharma GmbH;Freiburg;Duitsland

Intervention

Keyword: healthy volunteers, patients, Primary biliary cirrhosis, UDCA

Outcome measures

Primary outcome

SAFETY CRITERIA: Physical examination, ECG, vital signs, laboratory evaluations

and adverse events;

PHARMACOKINETIC PARAMETERS: Bile acids and bile acid metabolites;

PHARMACODYNAMIC PARAMETERS: Expressions of transporters and drug metabolizing

enzymes.

Secondary outcome

not applicable

Study description

Background summary

Primary Biliary Cirrhosis (PBC) is a presumed autoimmune disease of the liver. Administration of UDCA, has been shown to improve the biochemical parameters of cholestasis, to delay the histological progression of the disease and to delay the time to liver transplantation in patients suffering from PBC. Up to now, there are no reliable data available on the correlation of biliary enrichment of UDCA and serum pharmacokinetics during steady-state administration of UDCA. Comprehensive data of the relationship between biliary and serum acids in patients with PBC using modern analytical and clinical pharmacological methods is missing. The present study is designed to obtain such data for Ursofalk® film-coated tablets. Simultaneous investigations of UDCA enrichment and changes in bile acid composition in healthy volunteers and patients with PBC will be performed to assess the influence of the disease itself on these parameters. Within the scope of this study, the effect of UDCA on intestinal transport proteins and biotransformation phase I/II enzymes will be investigated in biopsies of the duodenal wall. In patients with PBC the prolonged administration of UDCA significantly decreased the probability of colorectal adenoma recurrence following removal. It appears possible that a reduced risk of colonic mucosal dysplasia in cholestatic liver disease during UDCA

treatment, as also observed in primary sclerosing cholangitis, is induced by modulation of fecal content in the small intestine due to UDCA-induced alterations of expression of transport proteins and phase I/II enzymes. Therefore, the present examination of duodenal biopsies for expression levels of key carriers and phase I/II enzymes before and during UDCA administration might contribute to unravel the pathophysiologic background of this promising clinical observation.

Study objective

To assess the bile acid composition of cystic bile and serum pharmacokinetics after a 3-week treatment with UDCA and to correlate pharmacokinetic parameter sof UDCA in bile and serum during steady state.
To compare the composition of bile acids and bile acid metabolites in serum before and after a 3-week treatment with UDCA.
To investigate the influence of UDCA on transport proteins and enzymes in the duodenal wall.
To compare the composition of cystic bile, the pharmacokinetics of bile acids and bile acid metabolites in serum as well as the influence of UDCA ontransportproteins and enzymes between patients suffering from PBC and healthy volunteers.
To assess the safety of UDCA treatment.

Study design

This is an open, non-randomized, parallel-group pharmacokinetic study carried out in 12 patients suffering from PBC and 12 healthy volunteers.

Intervention

All subjects: treatment with study medication (UDCA) for 21 days
Patients pretreated with UDCA: 6 weeks UDCA-washout

Study burden and risks

4-6 study visits, 2 x physical examinations, 2 x ECG, 3 x blood sampling for safety/serology, 17x blood-sampling for pharmacokinetics (during 24 hrs), 1 x abdominal sonography, 2 x gastroendoscopies, 2 x duodenal biopsies, treatment with UDCA (21 days), 1 diary for medication/adverse events (21 days), 6 weeks UDCA washout;
The study medication has a marketing authorization in the EU. After discontinuation of UDCA treatment in patients pretreated with UDCA a detoration of the liver parameters in blood may occur. The endoscopic investigation of the upper gastrointestinal tract is nowadays a low-risk routine procedure. The application of an indwelling cannula can be painful and may cause haematomae, in rare cases phlebitis. Blood withdrawal will presumably amount to

approximately 260 ml.

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

All subjects:
Male or female, adult, body mass index in the range of 18-30 kg/m2, able to give fully informed written consent, clinically acceptable vital signs and ECG.;Patients:
Positive anti-mitochondrial antibody testing, alkaline phosphatase or gamma-glutamyl-transpeptidase * 1.5 above normal at initial diagnosis and within 5 years prior to inclusion , histologically proven non-cirrhotic liver disease compatible wih PBC stage I, II, II-III and no reliable signs of portal hypertension such as esophageal varices or ascites and/or pylephlebectasia > 15 mm.;Volunteers:
Non-smokers, routine laboratory parameters within their normal range or deviations from

normal range not clinically relevant according to the investigator.

Exclusion criteria

All subjects:
Existing cardiac, hematological, renal, gastrointestinal (other than PBC) diseases and/or pathological findings which might interfere with the drugs' safety, tolerability, absorption, pharmacokinetics and/or endoscopy; other acute or chronic diseases which might affect absorption or metabolism of UDCA; existing disorders of the coagulation system or treatment with anticoagulants
or agents inhibiting thrombocyte aggregation; alcohol abuse; positive anti-HIV-test or HBs-Ag-test or anti-HCV-test; intake of cholestyramine or H2-antagonists within the last 3 days prior to first administration of study drug and during the study; intake of antacids within 12 hours prior to first administration of study drug and during the study; repeated intake of drugs which might interfere with gastrointestinal absorption and motility within the last 3 days prior to first administration of study drug and during the study; known allergic reactions to the active ingredients used or to constituents of the pharmaceutical preparations; acute inflammation of the gallbladder or bile duct system; obstruction of the bile ducts; acute hepatitis; patients/volunteers suspected not be able to understand or follow instructions; patients/volunteers in financial difficulties; blood donation or other blood loss of more than 400 ml within the previous 2 months; women of child-bearing potential without two independent methods of contraception.;Patients:
Any other hepatic disease of metabolic, viral and/or toxic origin, secondary biliary cirrhosis, other autoimmune hepatitis than PBC; clinically relevant pathological laboratory findings not related to hepatic disorder; histologically proven cirrhotic liver disease or total bilirubin > 3 mg/dl or reliable signs of portal hypertension; complete thrombosis of the portal vein; heavy smokers; pregnant/lactating women; intake of UDCA in the 6 weeks prior to Study Day 1; increases in at least two of the following five liver parameters by * 4 times the upper limit of normal after 4 weeks of UDCA wash-out: AST, ALT, *-GT, total bilirubin, alkaline phosphatase.;Volunteers:
History or clinical evidence of any cardiac, cardio-vascular, hepatic, cholangiolar, renal, pulmonary, endocrine, neurologic, infectious, gastrointestinal, hematological, oncological, psychiatric disease or emotional problems or any other clinical relevant condition, physical finding, laboratory test abnormality which, in the opinion of the Investigator, would pose a significant risk to the volunteer, invalidate the giving of the informed consent or limit the ability of the volunteer to comply with study requirements or interfere otherwise with the conduct of the study, any medication within the last 14 days prior to or during the conduct of the study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2007
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ursofalk 500 mg film-coated tablets
Generic name:	Ursodeoxycholic acid

Ethics review

Approved WMO Date:	24-04-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2009
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
EudraCT	EUCTR2006-003712-22-NL
CCMO	NL16377.018.07