Effects of cholestasis on pharmacokinetics

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Primary: To assess the effects of cholestasis on metabolism of five drugs, who are metabolized by 5 different CYP P450 isoforms.Secondary: To correlate the effect of cholestasis on drug metabolism with the effect of cholestasis on bile acid...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON38889

Source
ToetsingOnline

Brief title
Cholestase and pharmacokinetics

Condition

- Hepatic and hepatobiliary disorders

Synonym
icterus, jaundice

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bile acids, Cholestasis, Pharmacokinetics

Outcome measures

Primary outcome

The difference in area under the plasma concentration versus time curve (AUC)

for each drug following the oral administration of the drug cocktail prior to

ERCP in patients with cholestasis (A1) in comparison with the control situation

2 weeks after successful drainage has been achieved (A2).

Secondary outcome

The correlation between changes in AUC of the drugs and changes in AUC of

postprandial bile acids before and after biliary drainage.

Study description

Background summary

Hepatic metabolism of drugs is modulated by endogenous and exogenous factors. Experimental studies have demonstrated that bile acids influence the gene expression and activity of regulatory enzymes of cytochrome P450, next to their influence on bile acid metabolism itself. Patients with posthepatic cholestasis represent an unique human model for the excessive hepatic exposure to bile acids and their effects on hepatic metabolism of drugs and bile acids. After successful internal biliary drainage, these patients represent a model for the waning effect of these excessive bile acids. Therefore, we aim to assess the effects of posthepatic cholestasis, before and after biliary drainage, on hepatic drug and bile acid metabolism to elucidate the extent to which bile acids influence hepatic drug metabolism in humans.

Study objective

Primary: To assess the effects of cholestasis on metabolism of five drugs, who are metabolized by 5 different CYP P450 isoforms.
Secondary: To correlate the effect of cholestasis on drug metabolism with the

effect of cholestasis on bile acid metabolism

Study design

Prospective intervention study

Intervention

This study consists of two study days. Subjects will receive a single administration of a drug cocktail prior to (A1) and 2 weeks after (A2) successful biliary drainage by ERCP. The drug cocktail consists of 50 mg caffeine, 5 mg warfarin, 20 mg omeprazol, 20 mg metoprolol and 0.015 mgkg-1 midazolam. Pharmockinetic (PK) blood samples will be taken at t= 0, 2, 11,5, 15, 29, 41.5, 60, 90,135, 173, 180 and 195 minutes and 3.5, 4, 5, 7, 9 and 24 hours after administration of the drugs
A few hours after the drug cocktail, subjects receive a standardized liquid meal which contains 25% of daily recommended calories, after which some additional blood samples will be taken to assess bile acids, glucose and insulin.

Study burden and risks

The burden of this study includes two 12-hour hospital admissions after an overnight fast and two intravenous administrations of the drug cocktail. Blood samples will be drawn via a second intravenous catheter for pharmacokinetic (PK) analysis, metabolic analysis, monitoring of laboratory parameters and for pharmacogenetic analysis of liver enzymes. A total volume of 250 ml blood will be obtained. The risks for patients are low, since the cocktail consists of low, subclinical doses of drugs frequently used in daily clinical practice without adverse events.
This study will generate information regarding the drug metabolizing activity and bile acid metabolism during cholestasis and may therefore be of future benefit for patients with cholestasis using medication.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Bilirubin > 50 mmol/l, caused by posthepatic biliary obstruction
- Endoscopic Retrograde CholangioPancreatography (ERCP) has been scheduled
- > 18 years old

Exclusion criteria

- Diabetes Mellitus (both type 1 and 2)
- Cholangitis
- If a significant change in use of medication after ERCP is to be expected
- Use of omeprazole, warfarin, metoprolol, caffeine or midazolam (= medication of our probe cocktail) as standard treatment
- Use of herbal medicine or medication that inhibits or induces CYP3A4/5, CYP2C9, CYP1A2, CYP2C19, CYP2D6

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO Date:	29-07-2013
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

No registrations found.

In other registers

Register	ID
CCMO	NL44326.018.13