Effect of nutritional conditioning on the pharmacokinetics of acetaminophen

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To assess the effect of short term starvation and short term high fat diet on orally administered acetaminophen metabolism in healthy subjects.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38549

Source
ToetsingOnline

Brief title
Effect of nutritional conditioning on PK of APAP

Condition

- Other condition

Synonym
not applicable (see C21)

Health condition

farmacokinetiek van paracetamol, niet specifiek tbv een/meerdere aandoeningen

Research involving
Human

Sponsors and support

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

Intervention

Keyword: acetaminophen, nutrition, pharmacokinetics

Outcome measures

Primary outcome

Primary study endpoint is the difference in area under the plasma concentration versus time curve (AUC) for acetaminophen and six of its metabolites following the administration of the medication after 36 hours of starvation or after three days of a high fat diet in comparison with the control situation of an overnight fast.

Secondary outcome

Secondary endpoints include the difference in the PK parameters clearance, volume of distribution, absorption rate, mean residence time and elimination half-life. Furthermore, the effect of short term starvation and high fat diet in combination with APAP administration on glutathione metabolism will be studied.

Study description

Background summary

Acetaminophen is one of the most widely used drugs. Although safe at a therapeutic dose, an overdose can cause hepatotoxicity. Hepatotoxicity is induced by formation of toxic metabolites by several enzyme systems in the liver. The activity of many of these enzyme systems is modulated by nutritional factors. Although hardly studied in humans, there are indications from experimental studies that nutritional conditioning, i.e. the composition of the previous nutrition, influences acetaminophen metabolism. Therefore, nutritional conditioning may contribute to both inter- and intra-individual variations in acetaminophen metabolism and hence in acetaminophen induced toxicity.

Study objective

To assess the effect of short term starvation and short term high fat diet on orally administered acetaminophen metabolism in healthy subjects.

Study design

Open-label, single-dose crossover intervention study

Intervention

This study consists of three sequential interventions (n=9 subjects per intervention). The order of the interventions is determined by random assignment. Subjects will receive a single oral administration of 1000mg acetaminophen (1) after an overnight fast (controls), (2) after 36h of starvation or (3) a three day high fat diet.

Study burden and risks

The burden of this study includes a screening visit, three 8-hour hospital admissions, an overnight fast, a period of 36 h of starvation, three days of a high fat diet (a regular diet supplemented with 500ml of cream after supper) and three administrations of 1000mg acetaminophen. One urine sample will be taken to perform a urinary drug screening and during hospital admission 3x 8 hour urine will be collected to assess renal excretion of acetaminophen metabolites. Subjects will keep a diary of their regular diet during three days before the first hospital admission and will use the same diet in the three days before the second and third intervention, with exception of the fasting periods (overnight and 36h of starvation). Blood samples (36 samples of which 30 samples via an intravenous catheter) will be drawn for PK analysis (n=27), monitoring of laboratory parameters (n=8) and for pharmacogenetic analysis of CYP enzymes (n=1). A total volume of 121.5 ml blood will be obtained. The risks for the healthy volunteers are low. This study will generate information regarding the drug metabolizing activity of acetaminophen during fasting and after a high fat diet and may therefore be of future benefit for patients with differences in nutritional status using high dosed acetaminophen.

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

- Healthy (determined by an experienced physician) male of 18 years or older at the time of signing the informed consent
- Normal renal and liver function
- capable of giving written informed consent and to comply with the requirements and restrictions listed in the informed consent form

Exclusion criteria

- Major illness in the past 3 months
- gastrointestinal disease which may influence drug absorption
-abnormalities in ASAT/ALAT/bilirubin/gammaGT/AF laboratory data
-drug abuse or alcoholism (>3 units of alcohol per day)
- participation in another clinical trial in the past 12 months
- difficulty in donating blood or limited accessibility of a vein
- use of tobacco products (induction liver enzymes)
- (chronic) use of medication

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-02-2014
Enrollment:	9
Type:	Actual

Ethics review

Approved WMO Date:	06-01-2014
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	NL46677.018.13