Pharmacokinetics of intravenous acetaminophen and its metabolites in morbidly obese patients

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Primary objective: - To study the pharmacokinetics of acetaminophen and metabolites in morbidly obese patients and compare with normal weight patients. Secondary objectives: - To compare the pharmacokinetics of acetaminophen and metabolites in…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal therapeutic procedures
Study type	Observational invasive

Summary

ID

NL-OMON37478

Source
ToetsingOnline

Brief title
APAP study

Condition

- Gastrointestinal therapeutic procedures

Synonym
obesity or overweight

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Acetaminophen, Metabolism pathway's, Morbid obesity, Weight reduction

Outcome measures

Primary outcome

Clearance (total, glucuronidation, sulphation, CYP2E1 oxidation and unchanged) and volume of distribution of acetaminophen in morbidly obese patients in comparison with normal weight patients.

Secondary outcome

- Difference in clearance (total, glucuronidation, sulphation, CYP2E1 oxidation) and volume of distribution of acetaminophen in morbidly obese patients at the time of bariatric surgery and 0.5 * 2 year after bariatric surgery.
- Liver function tests (ASAT, ALAT, prothrombin time, gamma- GT, bilirubin, creatinine and albumin) in morbidly obese patients in comparison with normal weight patients.

Other endpoints that will be measured:

- Total body weight, length and fat (free) mass
- Insulin resistance: homa IR (fasting insulin and glucose levels)
- Lipid levels: free fatty acids, triglycerides, cholesterol
- Inflammation markers: TNF-alfa, IL-6, leptin, adiponectin en CRP
- Metabolomic profile

Study description

Background summary

Obesity represents one of the most important public health issues according to the World Health Organization. Despite increased pharmacotherapy among obese patients, there is a paucity of dosing guidelines for this population. Pharmacokinetic (PK) and pharmacodynamic (PD) studies are necessary to determine the appropriate dosing regimen as obese patients have a different body composition compared to normal-weight individuals, which influences especially the volume of distribution (Vd) and total clearance (Cl) of drugs [1] [2].

Acetaminophen is a frequently used analgesic in the peri-operative setting. Glucuronidation and sulphation are the main metabolic pathways; about 60% and 30% respectively [3] [4]. About 2% of acetaminophen is excreted unchanged in the urine. Approximately 5 -10% of acetaminophen is metabolized by cytochrome P450 to a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) [4]. CYP2E1 is the primary enzyme responsible for the formation of this toxic compound in humans [5] [6] [7]. NAPQI is immediately inactivated by conjugation with glutathione to a neutral metabolite and excreted as cysteine and mercapturic acid conjugates in urine [3].

Current literature consists of two studies in which the pharmacokinetics of acetaminophen in obese adults are investigated [8-9]. The volume of distribution (Vd) and clearance (Cl) are increased in obese patients in comparison with control patients [9]. However none of these studies examined the glucuronidation, sulphation and/ or oxidation (CYP2E1) pathway of acetaminophen in obese patients. Because one of this pathways is involved in acetaminophen toxicity, i.e. the CYP2E1 mediated pathway, it is important to explore the separate contribution of these different metabolism pathways to this increased clearance. Furthermore, these studies only examined the pharmacokinetics of acetaminophen in moderately obese adults in stead of the now frequently encountered morbidly obese adults.

In obesity glucuronidation is likely to be induced [10] [11]. Sulphation is not examined in obese humans. The activity of CYP2E1 is higher in obese patients in comparison with normal weight subjects [12] [13] [11] [14]. Liver fatty infiltration (NAFLD, non alcoholic liver disease) and insulin resistance may be the underlying cause of increased CYP2E1 activity in obese patients [11] [15].

Because of the possible higher Vd and higher Cl of acetaminophen in obese patients, this group of patients may need a higher loading and maintenance dose. However, the increased CYP2E1 pathway should be kept in consideration as CYP2E1 catalyses the formation of NAPQI.

The formation of NAPQI has only been investigated in obese rats. The clearance of the cysteine and mercapturic metabolites was increased by 56% after administration of a subtoxic dose of acetaminophen (303 mg/kg ideal body weight) [16]. This indicates an increase of the CYP2E1 pathway and formation of the metabolite NAPQI. To place the 56% increase into perspective; the total amount of CYP2E1 metabolism will be 7.5% in stead of the normal 5%. Also gluthatione will be present to inactivate NAPQI.

This study will investigate the pharmacokinetics of acetaminophen (total Cl and Vd) in morbidly obese patients. Specifically the different metabolic pathways of acetaminophen in morbidly obese adults will be investigated; glucuronidation, sulphation, CYP2E1 oxidation (measurable by cysteine and mercapturic metabolites) and unchanged acetaminophen. This will be compared with normal weight subjects, but also with the same patient group 0.5 - 2 years post surgery to determine whether the changes induced by obesity will be reversible after weight loss.

Study objective

Primary objective:
- To study the pharmacokinetics of acetaminophen and metabolites in morbidly obese patients and compare with normal weight patients.

Secondary objectives:
- To compare the pharmacokinetics of acetaminophen and metabolites in morbidly obese patients at the time of bariatric surgery and 0.5 * 2 year after bariatric surgery.
- To compare the safety of acetaminophen in morbidly obese patients with normal weight patients.
- Assess the influence of both demographic (age, sex) and physiologic covariates (body weight, insulin resistance, lipid levels and inflammation markers) on acetaminophen pharmacokinetics.
- To evaluate the metabolomic profile in morbidly obese patients and normal weight patients.

Study design

This is a prospective observational intervention study which will be performed in morbidly obese patients around bariatric surgery. A control group consisting of normal weight patients undergoing general surgery will also be included. According to study protocol patients of both study groups will receive an intravenous dose (2 g) of acetaminophen 45 minutes before surgery. Venous blood samples will be collected until 480 minutes after intravenous acetaminophen administration. In addition, 24 hour urine will be collected for both study groups. Samples for liver function tests will be withdrawn at 24 hours for these two groups and because blood withdrawal is already taking place at this

time point, one last blood sample will be taken for acetaminophen as well.

As after 0.5 * 2 years the bariatric patients will be at their weight loss optimum, these patients are invited to the hospital to participate in the second study visit. At the second study visit intravenous acetaminophen (2 g) will be administered and blood samples will be collected until 480 minutes. In addition, urine will be collected during the second study day.

Study burden and risks

There are no direct benefits of this study for the study patients. The results of the study will provide insight into different metabolic and elimination pathways of acetaminophen in morbidly obese patients. The potential risks associated with this study are minimal as we are using a drug that is part of our standard of care.
The dose which is used in this study is 2 g intravenous acetaminophen. Standard of care is 1 g acetaminophen orally before surgery. The reason for choosing a higher dose than standard of care is because of the quantification of the cysteine and mercapturic metabolite with the HPLC assay. Multiple studies show that a 2 g loading dose of intravenous acetaminophen is safe and effective [17] [18] [19]. Maximum plasma concentrations reached were far below the threshold for hepatotoxicity (150 *g/mL) and no hepatic adverse effects were measured within 48 hours of 2 g acetaminophen treatment [17]. In addition, the SPC text of acetaminophen reports that the toxic amount of acetaminophen administered as a single dose is 7.5 g. Moreover, Juhl et al showed that the analgesic efficacy of 2 g starting dose of intravenous acetaminophen is superior to recommended dose of 1 g in terms of magnitude and duration of analgesic effect for postoperative pain [18].
Furthermore increasing the dose of acetaminophen to 2 g allows for an extension in the dosing interval to 8 hours in stead of the normal dosing interval of 6 hours. The extension in dosing interval allows us to study for the pharmacokinetics of acetaminophen and metabolites, up to the 8 hours after dosing. After 8 hours of blood sampling the standard postoperative pain management procedure of acetaminophen will start (every 6 hours 1 g of acetaminophen).
A maximum amount of 76 millilitres of blood will be sampled from an indwelling venous catheter before, during and after surgery and one venipuncture at t = 24 hours. The catheter will be placed in addition to a regular intravenous catheter used for standard clinical care. The sampling of blood will have no influence on patient recovery.

The first study visit will take place around the bariatric surgery. For the second study visit the bariatric patients need to come back to the hospital, but this study visit can be combined with a routine post-operative follow up visit in the out-patient clinic. A second acetaminophen pharmacokinetic profile in the same individual after weight loss is essential to assess whether changes between morbidly obese patients and normal weight patients are reversible upon

weight loss.

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

Inclusion criteria for morbidly obese patients:
- BMI > 40 kg/m2 undergoing bariatric surgery.
- 18 -60 years old
- ASA physical classification of II or III
- All racial and ethnic groups will be included;Inclusion criteria for normal weight patients:
- BMI between 18 and 25 kg/m2 undergoing general surgery
- 18 -60 years old
- ASA physical classification of I, II or III

- All racial and ethnic groups will be included

Exclusion criteria

Exclusion criteria for all patient groups:
- Renal insufficiency identified by GFR < 60 ml/min/1.73m2
- Liver disease identified by liver function tests: ASAT, ALAT, prothrombin time, *-GT, bilirubin, creatinine, albumin and alkaline phosphatase (ALP) (> 3 times upper limit of normal values)
- Patients with Gilbert-Meulengracht syndrome
- Chronic alcohol intake or use of alcohol within last 72 hours
- Pregnancy or breastfeeding
- Patients who are treated with drugs know to affect CYP2E1 (inhibition: dithiocarb and disulfiram. Induction: isoniazid) and UGT (UDP-glucuronyltransferases) (induction: estradiol-containing contraceptives, carbamazepine, phenobarbital, phenytoin, mesuximide, oxcarbazepine, rifampicin, primidone, atazanavir / ritonavir, lopinavir / ritonavir, olanzapine, retigabine , nevaripine, efavirenz, saquinavir, nelfinavir, lamotrigine, felbamate, zonisamide, bupropion. Inhibition: valproic acid)
- Diabetes mellitus type II patients
- Smoking
- Acetaminophen intake before the study (24 hours before study)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-11-2012
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tylenol
Generic name:	acetaminophen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-04-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-06-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2012-000956-32-NL
CCMO	NL39958.100.12