Peri- and postoperative subcutaneous adipose tissue cefazolin determination using microdialysis in morbidly obese and non-obese patients

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

Summary

ID

NL-OMON36673

Source
ToetsingOnline

Brief title
MICK (Microdialysis study for the Investigation of Cefazolin Kinetics)

Condition

- Other condition
- Gastrointestinal therapeutic procedures

Synonym
prevention of wound infection in obese patients, wound infection after surgery in obese patients

Health condition

Obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Nuts OHRA financiert de bepaling van cefazolin en een onderzoeker

Intervention

Keyword: cefazolin, microdialysis, Morbid obesity, tissue concentration

Outcome measures

Primary outcome

Primary endpoints:

1. Cefazolin concentrations in subcutaneous adipose tissue

2. Total and unbound cefazolin concentration in plasma

3. Cefazolin unbound subcutaneous tissue/unbound plasma concentration ratio

differences between morbidly obese and non-obese patients

Secondary outcome

Secondary endpoints:

1. Anti-factor Xa concentrations: 11 samples in non-obese patients, 3 in

morbidly obese patients) in blood following nadroparin

Tertiary endpoints:

1. Pharmacokinetic parameters of cefazolin

2. Pharmacodynamic parameters of nadroparin

3. The occurrence of postoperative SSI

4. The occurrence of deep vein thrombosis /pulmonary embolism

Study description

Background summary

Morbid obesity prevalence is rising worldwide. As a consequence weight reducing therapies such as bariatric surgeries including gastric banding, and -bypass surgery and sleeve-gastrectomy are rising as well. Complications of these interventions include, among others, surgical site infections (SSI), as obesity itself is a risk factor for SSIs. In an earlier study in 20 obese patients (POP-2 study, NCT01097148) 2 patients developed an SSI despite the fact that unbound cefazolin concentrations were all above the minimal inhibitory concentration (MIC90) of S. Aureus of this hospital until 2 hours after surgery. Reduced perfusion of adipose tissue in obese patients, resulting in subcutaneous cefazolin concentrations below MIC, could be a plausible explanation for this controversy. To test this hypothesis, we aim to determine cefazolin concentrations in subcutaneous adipose tissue and investigate the relation to unbound and total cefazolin concentrations in morbidly obese patients undergoing (bariatric) surgery.
Currently, there are no specific reports providing information on cefazolin distribution in non-obese patients. Comparing the unbound cefazolin plasma and cefazoline subcutaneous concentration in morbidly obese and non-obese will provide insight on what factors are of influence on the distribution of cefazolin (is it bodyweight, tissue perfusion, distribution of adipose tissue, etc?). When factors of influence are identified, it will be possible to predict the cefazoline subcutaneous concentrations from plasma cefazolin concentrations. This way we will be able to adequately adjust standard cefazoline doses for the specific patient that needs it. To accomplish this important predictive step, we will determine unbound and total cefazolin concentrations in plasma and subcutaneous adipose tissue in non-obese patients as well. All observations will be used to construct a population pharmacokinetic (PK) model and to define an adequate cefazolin dosing regimen in the morbidly obese population.
Other complications of weight reducing surgery include deep vein thrombosis and pulmonary embolism. In the earlier POP-2 study we determined anti-factor Xa concentrations in response to subcutaneous administration of nadroparin in morbidly obese patients and found a large variation in anti-factor Xa concentrations over time. It is unknown whether this variation can be explained by the variability in bodyweight, clearance and/or in subcutaneous resorption. Therefore anti-factor Xa concentrations in non-obese patients are urgently needed. Data of both morbidly obese and non-obese patients will allow investigation into what extent the nadroparin pharmacokinetics and/or -dynamics of these drugs are affected in morbidly obese patients, thereby reducing the risk of deep venous thrombosis/pulmonary embolism and/or excessive bleeding complications. Findings will be used to construct a population pharmacodynamic (PD) model and to define an adequate nadroparin dosing regimen in the morbidly

obese population.

Study objective

The primary objective of this study is to investigate target site penetration of cefazolin in morbidly obese patients. Also, we aim to investigate whether cefazolin plasma concentrations are predictive of subcutaneous (target) cefazolin concentrations and what factors are of influence on the distribution of cefazolin (tissue perfusion, bodyweight, distribution of adipose tissue; etc.). For this reason, we will determine unbound and total cefazolin concentrations in plasma and subcutaneous adipose tissue in non-obese patients as well and we will compare the observations between morbidly obese and non-obese patients. All observed cefazolin concentrations will be analyses using nonlinear mixed effects modelling in order to develop a population PK model.
Secondary objective of the study is to collect anti-factor Xa concentrations in non-obese patients. Together with anti-factor Xa plasma concentrations obtained in the POP-2 study and 3 additional samples in morbidly obese patients in the current study, a population PD model will be constructed.
The influence of patient and procedure-related covariates on pharmacokinetic and -dynamic parameters will be investigated. Finally, with these two models, we aim to develop evidence-based dosing schedules for both nadroparin and cefazoline in morbidly obese patients.

Study design

Prospective observational expolarory pilot study

Study burden and risks

Clinical microdialysis is a safe and reproducible technique for studying drug distribution in patients. The burden of this study is minimal and consists of the insertion of a microdialysis probe in the ride side of the patient's abdomen 2 hours before until 2 hours post surgery. Insertion of the probe is comparable to an intra-muscular injection.
For the non-obese patient group an arterial line will be placed for the purpose of this study. We believe that the extra burden and risk associated with this procedure is acceptable, as anesthesiologist in this hospital are highly experienced in placing arterials lines (due to large scale open heart surgery in the St. Antonius Hospital). Furthermore, as the arterial line will be placed after induction of anaesthesia, the patient will not experience local pain due to the placement of the arterial line involved.
A maximum amount of 50 millilitres of blood will be sampled from an indwelling arterial line during and after surgery. The arterial line will be kept in place approximately 2 hours longer than usual for the morbidly obese patients and 4 hours longer for the non-obese patients.

During surgery the cardiac output will be measured using two different monitoring systems, the NICOM® (Cheetah Medical) and Vigileo (Edwards Lifesciences). These non-invasive cardiac output measurements do not represent additional burden of the patient.

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

8 morbidly obese patients Body Mass Index > 40 kg/m2 undergoing bariatric surgery, 21-60 years old. We will stratify subjects to 4 weight groups: 100-125 kg; 125-150 kg; 150-180 kg; >180 kg.
8 non-obese adults (BMI >19<30; age 21-60 years) undergoing surgery which includes cefazolin and nadroparin administration perioperatively and a postoperative stay at the post anesthesia care unit (PACU).

Exclusion criteria

Pregnancy, breastfeeding, known allergy for cefazolin/nadroparin, known ejection fraction of <35%, renal insufficiency, hematochromatosis.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-12-2010
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	09-11-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-05-2011

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-07-2011
Application type:	Amendment
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
CCMO	NL33065.100.10