Optimal dosing of antibiotics in (morbidly) obesee patients

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29597

Source
NTR

Brief title
AMIGO

Health condition

(Morbid) Obesity, Pharmacokinetics, Antibiotics, Infective diseases

Sponsors and support

Primary sponsor: St. Antonius Hospital, Nieuwegein
Source(s) of monetary or material Support: ZonMW GGG (Goed Gebruik Geneesmiddelen)

Intervention

Outcome measures

Primary outcome

Primary endpoint is clearance (Cl) of gentamicin, tobramycin, vancomycin or ciprofloxacin in obese participants versus normal weight participants. Other primary endpoints are volume of distribution (Vd) and 24-hour renal clearance for all four drugs and oral bioavailability (F) for ciprofloxacin in obese participants versus normal weight participants.

Secondary outcome

Influence of covariates (total bodyweight, lean bodyweight, fat mass, gender, length, age, creatinine, metabolomic profile, GFR) on primary parameters of interest (i.e. clearance and volume of distribution).

Study description

Background summary

Infectious diseases are a major public health threat. In general, adequate treatment with antibiotics (i.e. an effective dose) is
essential for the survival of patients with infectious diseases. For many antibiotics, available evidence on how to adjust the dose
in (morbid) obesity in clinical practice is insufficient, such despite the fact that both the prevalence of (morbid) obesity
(BMI>(40/)30 kg/m2) and the bodyweights itself are increasing worldwide. Obesity and particularly morbid obesity are known to
influence different pharmacokinetic parameters such as clearance and volume of distribution, even though exact quantification is
still warranted for many drugs.

For severe life-threatening infections, aminoglycosides and vancomycin are important antibiotics. Fluoroquinolones (especially
ciprofloxacin) play an important role in the treatment of moderate to severe infections, ranging from soft tissue infections to
infections of the pulmonary, gastrointestinal or urogenital tract.
For aminoglycosides and vancomycin there is a distinct relation between serum concentrations and both efficacy and toxicity
(e.g. nephrotoxicity). Timely attainment of target concentrations is of utmost importance and has been recognized as key element
in the surviving sepsis campaign.

In daily clinical practice, dosing in morbidly obese patients is still based on dose guidelines for
normal weight patients after which Therapeutic Drug Monitoring (TDM) is applied to adjust the subsequent doses. Using this
approach, there may be a substantial delay in time to attain target concentrations known to lead to optimal effect and prevent
toxicity. This inability to upfront predict the adequate dose puts the morbidly obese patients

at increased risk of failure of therapy
or toxicity. This is also the case for fluoroquinolones, where in general practice TDM is not routinely performed and (morbidly)
obese patients are at risk for failure of therapy when serum concentrations are too low. For these reasons, evidence on the
pharmacokinetics of aminoglycosides, vancomycin and ciprofloxacin in (morbidly) obese patients is highly warranted in order to
provide a basis for a dosing guideline for this special patient population.

Currently, dosing guidelines for these antibiotics are lacking specific dose adaptations for (morbidly) obese patients, since there
is a paucity of data in available literature on (the pharmacokinetics) these antibiotics that can actually be used to guide dosing.
This is due to several reasons, with among others are the application of now uncommon dosing frequencies and target
concentrations of these antibiotics (i.e. studies on three times daily dosing of aminoglycosides with only 8h sampling schemes,
whereas currently once daily dosing with 24 h sampling is applied), outdated definitions of obesity (i.e. drugs have been studied
in nowadays only mildly obese patients), inadequate characterization of the pharmacokinetics (i.e. due to limited number of
samples per individual (use of TDM data)) and/or other suboptimal methodology (i.e. unavailability of non-obese controls)). For
ciprofloxacin, there is one study available on intravenous dosing without information on oral absorption while sampling was done
over 6h instead of 8h making extrapolation to dosing guidelines difficult.

In conclusion, there is a clear lack in the available
literature to design dosing guidelines that can be expected to result in predictable drug concentrations that correlate with optimal
efficacy and safety in this special patient population in clinical practice.

Study design

Blood samples will be collected until 24 hours post-infusion. For vancomycin, we will also obtain a 48 hour sample if the participant is still admitted, and for ciprofloxacin, we will only obtain samples to 12 hours post administration. During 24 hours post-administration, urine is collected for determination of creatinine to determine the GFR. Serum creatinine concentration is measured before (for all participants) and 24 hours (for participants receiving gentamicin, tobramycin or vancomycin as a safety parameter) after administration of the study drug.

Intervention

In this study, the intervention consists of the administration of one dose of the investigational drug (gentamicin, tobramycin, vancomycin or ciprofloxacin). In the case of ciprofloxacin, the administration of ciprofloxacin PO will be 3 hours later followed by a one dose of ciprofloxacin IV.

Venous blood samples will be collected until 24 hours after dosing. For vancomycin, we will also obtain a 48 hour sample if the participant is still admitted, and for ciprofloxacin, we will only obtain samples to 12 hours post administration. Renal function will be checked just before and 24 hours after administration of the study dose using serum creatinine. In addition, 24 hour urine will be collected for both study groups. Urine will be collected when the participant has to void. Time of collection and urine volume will be reported and stored separately. One blood sample will be drawn to assess metabolomics.

Contacts

Public
St. Antonius Hospital Nieuwegein

C.A.J. Knibbe
Koekoekslaan 1,

Nieuwegein 3430 EM
The Netherlands
Tel: 088 - 320 72 25
Scientific
St. Antonius Hospital Nieuwegein

C.A.J. Knibbe
Koekoekslaan 1,

Nieuwegein 3430 EM
The Netherlands
Tel: 088 - 320 72 25

Eligibility criteria

Inclusion criteria

Inclusion criteria for (morbidly) obese participants:

- Indication for bariatric surgery (i.e. BMI > 40 kg/m2 or BMI > 35 kg/m2 with additional risk factors). Bariatric surgery includes the following: laparoscopic gastric bypass surgery or laparoscopic sleeve gastrectomy. We will equally (and in case of ciprofloxacin, with 2 or 3 patients per group) stratify subjects to 4 weight groups: 100-120 kg, 120-145 kg, 145-170 kg and >170 kg.;

- Participants between 18 - 55 years old;

- ASA physical classification of II or III;

- Participant is able and willing to sign the Informed Consent before screening evaluations.

Inclusion criteria for controls (normal weight participants):

- BMI between 18 and 25 kg/m2;

- Participants between 18 - 55 years old;

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Renal insufficiency identified by eGFR < 60 ml/min/1.73m2;

- Known allergy to the administered drug;

- Recent use of the study drug (up to 7 days before administration of the study drug);

- Treatment with the concerning study drug up to 7 days before administration of the study drug.

- Pregnancy or breastfeeding. This is an exclusion criteria for bariatric surgery as well (participants are informed by their surgeon and bariatric nurse). Women of childbearing potential using contraception are allowed to participate in the study.

Specific exclusion criteria for participants receiving an aminoglycoside or vancomycin:

- Participant who are treated with known nephro- or ototoxic drugs (immunosuppressants, antivirals, antineoplastic agents, ACE-inhibitors, diuretics, aminoglycosides, vancomycin and/or NSAIDs) up to 7 days before administration of the study drug.

Specific exclusion criteria for participants receiving ciprofloxacin:

- Known liver disease identified by liver function tests: ASAT, ALAT, prothrombin time, ã-GT, bilirubin, or alkaline phosphatase (ALP) (> 3 times upper limit of normal values)

- Known prolonged QT-interval or participants that use drugs that are known to prolong the QT-interval (based on the list published by CredibleMeds®, formerly known as AZCERT)

- Participants that use drugs that are known to be metabolized by CYP1E2 or CYP3A4 or influence gastric emptying (see Appendix 1)

- Epilepsy

- Smoking

- Myasthenia gravis

- Porphyria cutanea tarda

- Psychoses in history

For healthy volunteers a few extra prohibitions apply to participation (these are standard prohibitions employed in the CRCN):

- Water is allowed as desired except for one hour before and one hour after administration of study medication.

- From four hours after dosing until release of confinement, consumption of available beverages is free and meals are standardized in regard to consumption and time of administration.

- Subjects may not consume alcoholic beverages from 24 hours before until 48 hours after administration of study medication.

- Subjects may not use grapefruit containing food or juice, or St John’s worth, from 7 days before until the end of the study.

- The use of any medication (including herbal remedies, multivitamins, magnesium- and

calcium-containing supplements, acetaminophen, etc.) is prohibited during the entire study including two weeks prior to the start of the study.

- Female subjects of childbearing potential without adequate contraception, e.g. hysterectomy, bilateral tubal ligation, (non-hormonal) intrauterine device, total abstinence, double barrier methods, or two years post-menopausal. They must agree to take precautions in order to prevent a pregnancy throughout the study period. Male subjects should also use contraceptive methods in order to avoid pregnancy of their partners during the study period.

- Subjects are to refrain from strenuous exercise of all types while at the clinical research centre and at the day prior to administration of study medication.

- Subjects are not allowed to lie down without permission from one hour before until 4 hours after dosing of oral ciprofloxacin because body position and posture may influence physiological characteristics such as dissolution and (the rate of) absorption of ciprofloxacin.

- Subjects are not allowed to smoke at the clinical research centre.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-07-2016
Enrollment:	102
Type:	Anticipated

Ethics review

Positive opinion

Date:	15-08-2016
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 46981
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL5885
NTR-old	NTR6058
CCMO	NL52260.100.16
OMON	NL-OMON46981

Study results