DosemeLOL - Exploring differences in metoprolol concentrations between sexes, a pilot study

Published: 14-04-2025
Last updated: 28-04-2025

The main (primary) objective is to study the influence of sex on the pharmacokinetics (PK) of metoprolol in patients after CABG with heart valve surgery and patients with a STEMI/NSTEMI who are prescribed a standard dosage of metoprolol as part of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON57425

Source
ToetsingOnline

Brief title
DoseMeLol

Condition

- Cardiac arrhythmias
- Cardiac therapeutic procedures

Synonym
Atrial fibrillation, Coronary artery bypass grafting

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: support van kosten metoprolol

concentraties in bloed door Antonius Onderzoeksfonds

Intervention

Keyword: Gender, Metoprolol, Pharmacokinetics

Outcome measures

Primary outcome

The main study endpoint is the area under the time-concentration curve (AUC) of metoprolol on day three after CABG with heart valve surgery and any day after STEMI/NSTEMI in female versus male patients (called the day of the PK evaluation). Other primary endpoints are pharmacokinetic parameters including clearance (CL), volume of distribution (Vd), biological availability (F), absorption rate (Ka), maximum concentration (Cmax) and time to maximum plasma concentration (Tmax). For patients after CABG with heart valve surgery, postoperative day three is selected because on day 1 and 2 after surgery, absorption may be hampered.

Secondary outcome

The secondary study endpoints are the effects of metoprolol, i.e. absolute and delta heart rate, heart rhythm and blood pressure, and the occurrence of side effects such as hypotension, bradycardia, fatigue, dyspnea d*effort, cold hands and feet, Raynaud syndrome, dizziness, headache, nausea, vomiting, diarrhea and obstipation in female versus male patients on the day of PK evaluation, at discharge and at the first and second postoperative outpatient clinic visit.
Other secondary endpoints are the need and reason for dose adjustments compared to the starting dose or need for discontinuation of treatment at these time points. Besides sex, the influence of other patient characteristics like age,

indication and CYP2D6 genotype on the PK, effects and side effects are

explored.

Study description

Background summary

Metoprolol is a commonly used beta-blocker, that is used for many indications including hypertension, prevention of atrial fibrillation (AF), angina pectoris, cardiac failure and migraine.
In women treated with metoprolol, a stronger effect on heart rate and blood pressure, more side effects and higher blood concentrations have been reported compared to men. While guidelines of the European Society of Cardiology state that the dosage of cardiovascular drugs should be adjusted in women, there is however, to date, no guidance on how to adjust the dose of metoprolol at start or during treatment.

After cardiac surgery, a standard dose of metoprolol, 25 mg twice a day, is given to all patients for the prevention of atrial fibrillation for a duration of three months. To date there is insufficient knowledge on the pharmacokinetics (PK), effects and side effects of this dose between men and women. Similarly, in patients with an acute coronary syndrome (ACS), a standard dose of metoprolol is started on indication in men and women. Therefore, the aim of this study is to gain insight in the effect of sex on the PK, the effects and side effects of metoprolol in a 2-population study, i.e. 1. when given a standard dose after coronary artery bypass surgery (CABG) with heart valve surgery for three months and 2. after acute coronary syndrome (ACS, i.e. STEMI or NSTEMI).

Study objective

The main (primary) objective is to study the influence of sex on the pharmacokinetics (PK) of metoprolol in patients after CABG with heart valve surgery and patients with a STEMI/NSTEMI who are prescribed a standard dosage of metoprolol as part of standard of care. The secondary objective is to determine the influence of sex on the effects and side effects of metoprolol including need for dose adjustment or interruption. In these analyses, besides the influence of sex, other patient characteristics like age, indication and CYP2D6 genotype are explored.

Study design

The study is a low intervention clinical trial.

While patients undergoing a CABG with heart valve surgery will have a central venous catheter (CVC) and arterial line as part of standard of care, STEMI/NSTEMI patients will receive an extra venous catheter for blood sampling for the purpose of the study. On the day of the PK evaluation, i.e. day three after CABG surgery or any day after STEMI/NSTEMI, patients will be asked to fasten from two hours prior to the morning dose of metoprolol until four hours after this dose. The first blood sample will be taken right before the dose of metoprolol in the morning and around 12 hours after the evening dose (trough sample). For standardization, metoprolol will be taken with 50 ml of water after which the patient is asked to remain in upright position for 30 minutes. Over 12 hours, twelve blood samples (3ml) will be taken to determine the concentration of metoprolol. At all sample moments, heart rate, heart rhythm and blood pressure will be recorded. On the same day a blood sample will be taken to determine CYP2D6 genotype. For both groups, at discharge, at the routine visits around 2-3 weeks and 6-8 weeks after discharge, the metoprolol dose (changes) or need for treatment interruption are monitored together with effects and side effects of metoprolol.

Study burden and risks

All patients receive standard treatment and medication after either CABG with valve surgery or STEMI/NSTEMI, including start of treatment with a standard dose of twice a day 25 mg metoprolol tartrate and measuring blood pressure and heart rate regularly at ICU or ward. In the CABG with valve surgery group the already placed arterial line will be used to collect blood samples. In patients in the STEMI/NSTEMI group, a venous catheter will be placed to collect blood samples. Thirteen blood samples are taken during the PK evaluation part of this study during hospital stay, this amounts to 39 mL in total. In addition, patients are asked to fast from two hours prior to the morning dose of metoprolol at 6:00 am until four hours after this dose, which will delay breakfast with 2 hours. All other data collection is part of standard of care. Follow up after 2-3 weeks is also part of standard care, therefore no extra hospital visits are necessary. Patients will not receive any personal benefits from this trial. The results of this study may be used to improve treatment with metoprolol for future patients after CABG with valve surgery or STEMI/NSTEMI, with special attention to possible dose differences based on sex (and/or other covariates), therapeutic drug levels differences and reduction of side effects, successively.

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

Indication for metoprolol tartrate 25mg twice a day, being male or female, aged >= 60 years, <= 85 years

Exclusion criteria

Contraindication or intolerance for metoprolol, diseases or patient characteristics which influences or reduces the absorption for metoprolol

Study design

Design

Study phase: 4

Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2025
Enrollment:	24
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-04-2025
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
CCMO	NL88311.100.24