Pharmacokinetics of morphine and oxycodone in frail elderly undergoing cardiac surgery

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Primary: - To determine the pharmacokinetics and pharmacodynamics of morphine, oxycodone and its metabolites in frail elderly undergoing cardiac surgery. Secondary: - To assess the influence of covariates such as frailty, serum creatinine,...

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

Summary

ID

NL-OMON55041

Source
ToetsingOnline

Brief title
AWARE II

Condition

- Cardiac therapeutic procedures

Synonym
CABG, cardiothoracic surgery

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: R&D Anesthesie

Intervention

Keyword: Frail, Morphine, Oxycodon, Pharmacokinetics

Outcome measures

Primary outcome

Primary endpoints of this study are the pharmacokinetic parameters of morphine, oxycodone and metabolites in blood in frail patients. Pharmacokinetic parameters are clearance , volume of the central compartment, volume of the peripheral compartment, volume of distribution

Secondary outcome

* Pain according to Numeric Rating Scale (NRS)

* Postoperative opioid consumption in the first 5 postoperative days

* Vital signs by continuous monitoring (SpO2, respiratory rate, blood pressure)

* Side effects of opioids (nausea, vomiting, pruritus, constipation)

* Delirium according to delirium observation screening (DOS)

* Sedation according to sedation observation scale

Study description

Background summary

Opioid analgesics such as morphine and oxycodone are routinely used in the treatment of moderate to severe pain after cardiac surgery. However, the treatment of postoperative pain in elderly patients may be complicated by a number of factors, such as an increased risk of age and disease related changes in physiology, interactions between disease and medication, and polypharmacy, resulting in variability in analgesic response. Age is a significant predictor of opioid-related side effects, with patients older than 60 years having a two- to eight-fold increased risk of respiratory de-pression and falls and fractures. Frailty further increases this heterogeneity but its effects on pha-macokinetics and pharmacodynamics of drugs and metabolites are relatively

poorly studied. Current treatment guidelines advocate a *start low and go slow* approach to analgesic dosing in older patients, particularly in the treatment of frail older patients, because of fear of sedation and respir-atory depression. In practice, however, this dosing strategy is often interpreted as "start low, stay low", giving the impression that this population is at risk for inadequate analgesia, delirium and chronic pain. Despite increasing studies examining the implications and consequences of frailty for a range of medical outcomes, frail older people have been significantly underrepresented in clinical trials, including those designed to investigate optimal pain management strategies. Therefore, evidence-based management of postoperative pain in the frail elderly patient is very limited.

Study objective

Primary:
- To determine the pharmacokinetics and pharmacodynamics of morphine, oxycodone and its metabolites in frail elderly undergoing cardiac surgery.
Secondary:
- To assess the influence of covariates such as frailty, serum creatinine, Glomerular Filtration Rate (GFR) on the pharmacokinetics of morphine and oxycodone.

Study design

Single center observational cohort study

Study burden and risks

Preoperative frailty screening is part of routine care for older cardiac surgery patients at St. Antonius hospital and is no additional burden for study patients. Patients will receive a standardized anesthetic regimen in which routinely 10 mg intravenous morphine is administered at the end of surgery. Blood samples will be taken from an intravenous catheter and an arterial line, which are routinely inserted for drug/ fluid administration and invasive continuous monitoring of arterial blood pressure during cardiac surgery. In this study postoperative blood samples will be taken during postoperative stay in the Intensive care Unit (phase 1) and thereafter in the general ward (phase 2) to determine the pharmacokinetics and pharmacodynamics of morphine, oxycodone and its metabolites.
Phase 1: After cardiac surgery patients are admitted to the Intensive Care Unit (ICU) where they routinely will receive continuous intravenous infusion of morphine. During admission in the ICU blood samples will be taken from an indwelling arterial line, which will be removed upon discharge to the general ward. In total 10 samples with 5 ml extra blood will be taken to determine the pharmacokinetics of morphine and metabolites.

Phase 2: After discharge from the ICU to the general ward patients will receive 2 times a day 5 mg oxycodone according to a standardized postoperative pain protocol. Next, oxycodone blood samples will be taken up to 12 hours after the last administration from an indwelling intravenous catheter. A total of 6 samples of 5 ml will be taken during admission to the ward. No extra punctures are necessary to collect these blood samples. In total 80 ml extra blood will be taken from patients, which leads to a minimal additional burden for patients.
Furthermore, side effects of opioids such as nausea, vomiting, pruritus will be noted. Vital signs (e.g. (SpO2, PR, RR) will continuously be monitored after patients are discharged from the ICU to the general ward. Finally, a delirium score will be done. This will lead to a minimal additional burden. There are no further risks involved.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Adult patients *70 years undergoing elective cardiac surgery
2. Frailty, defined by the presence of at least two of the following characteristics:
- Impaired gait speed or hand grip strength
- Risk for malnutrition
- Impaired cognition
- Dependent living
- Impaired physical functioning
- Polypharmacy
- Impaired health related quality of life

Exclusion criteria

Patients undergoing emergency cardiac surgery
Patients undergoing transcatheter aortic valve replacement or mitral valve repair.
Contraindication for morphine and/or oxycodone
No informed consent

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2020
Enrollment:	40

Type:	Actual

Ethics review

Approved WMO Date:	05-08-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-05-2021
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	NL71713.100.20

Study results

Date completed:	12-10-2021
Actual enrolment:	34