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Interest of Naloxegol in the Recovery of Bowel Transit after Cardiac Surgery:

A Randomized, Double-Blind, Controlled Trial.

Time to Transit Recovery After Treatment with Naloxegol in Cardiac Surgery Intensive Care Trial

« TRANSIT »

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING A MEDICINAL PRODUCT

GENERAL INFORMATION

Protocol Code Number	2019/09
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1. ABBREVIATIONS

AMM: Marketing Authorization

ANSM: French National Agency for the Safety of Medicines and Health Products

ARC: Clinical Research Associate

BPC: Good Clinical Practices

BPF: Good Manufacturing Practices

CEC: Cardiopulmonary Bypass

CMC: Medical-Surgical Center

CNIL: French National Commission for Information Technology and Civil Liberties

CPP: Committee for the Protection of Persons

DFG: Glomerular Filtration Rate

DSUR: Development Safety Update Report

ECG: Electrocardiogram

EI: Adverse Event

EIG: Serious Adverse Event

EMA: European Medicines Agency

EVA: Visual Analog Scale

FC: Heart Rate

IDE: Registered Nurse

IV: Intravenous

MDRD: Modification of Diet in Renal Disease

mITT: Modified Intention to Treat

MR: Reference Methodology

NVPO: Postoperative Nausea and Vomiting

PAS: Systolic Blood Pressure

RCP: Summary of Product Characteristics

SNC: Central Nervous System

SpO2: Pulse Oxygen Saturation

SUSAR: Suspected Unexpected Serious Adverse Reaction

TA: Blood Pressure

UEM: Morphine Equivalent Units

USC: Continuous Care Unit

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. Study Context

Digestive complications following cardiac surgery are frequent and worsen patient prognosis. Paralytic ileus and Ogilvie syndrome are among these complications. They represent a real management challenge in intensive care, inducing morbidity-mortality, extended hospital stays, and significant postoperative costs. Few treatments appear effective for bowel transit recovery other than neostigmine, which has non-negligible side effects, particularly cardiac.

After cardiac surgery, opioid analgesics are frequently used to relieve pain, particularly sternotomy pain. Through their pharmacological effect, they contribute to postoperative paralytic ileus. Opioid receptors are distributed throughout the central nervous system, where they are involved in pain perception, but also peripherally, including in the mesenteric nervous system where they regulate peristalsis. Opioid receptor antagonists are therefore a prime target.

Naloxegol is a peripherally acting opioid receptor antagonist in tablet form, from the alvimopan family. It was designed to antagonize peripheral, but not central, effects of opioids at therapeutic doses. It is a substrate of cytochrome P450 and CYP3A4, rapidly absorbed with a mean time to maximum plasma concentration of 2 hours. Following once-daily administration, steady-state plasma concentrations are reached within 2-3 days with minimal accumulation. The main elimination route is hepatic, with minimal renal excretion.

Research hypothesis: Adding naloxegol pre- and postoperatively in cardiac surgery could reduce the time to bowel transit recovery and the rate of digestive and respiratory complications, as well as the duration of intensive care stay, without negative effects on analgesia.

2.2. Research Objective

The objective of this study is to demonstrate that the administration of naloxegol in the perioperative period of cardiac surgery reduces the duration of postoperative ileus.

2.3. Summary of Benefits and Foreseeable Risks

2.3.1. Expected Benefits for the Patient

Expected benefits include a reduction in the rate of digestive complications, discomfort, pneumonia rate, and duration of hospitalization.

2.3.2. Foreseeable and Known Risks

The main risks associated with this clinical trial are related to the administration of naloxegol. In pooled clinical trial data, the most frequently reported adverse effects with naloxegol (≥5%) are: abdominal pain, diarrhea, nausea, headache, and flatulence. The majority of gastrointestinal adverse effects were evaluated as mild to moderate, occurred at the start of treatment, and resolved upon continuation.

2.4. Description of the Study Population

Adult patients scheduled for cardiac surgery under cardiopulmonary bypass (CPB).

3. RESEARCH OBJECTIVES

3.1. Primary Objective

To evaluate the effect of perioperative naloxegol administration in cardiac surgery on the duration of postoperative ileus.

3.2. Secondary Objectives

- Evaluate the effect of naloxegol on digestive complications
- Evaluate the effect of naloxegol on respiratory complications
- Evaluate the rate of infectious complications
- Verify the maintenance of normal analgesia
- Compare total hospitalization durations
- Compare lengths of stay in intensive care unit and continuous care unit (CCU)

4. JUDGMENT CRITERIA

4.1. Primary Endpoint

Time (in hours) to bowel transit recovery after cardiac surgery, defined as the duration in hours between the first anesthetic induction and the emission of the first significant stool (approximately 100g as judged by the nursing assistant or nurse in charge of the patient, blinded to treatment).

The number of patients who received macrogol and the number who received picosulfate will be indicated for each arm.

4.2. Secondary Endpoints

Related to Secondary Objective 1 – Digestive Complications Rate:

- Intra-abdominal pressure measured via an adapted urinary catheter on Day 1 and Day 2 minimum, until measurement is feasible (cmH2O)
- Vomiting
- Ogilvie syndrome defined by an occlusive syndrome >72h and cecal distension >8cm
- Mesenteric ischemia documented via abdominal imaging, colonoscopy, or laparoscopy
- Need for colonoscopy
- Placement of nasogastric tube
- Intolerance to solid food at Day 2

Related to Secondary Objective 2 – Respiratory Complications Rate:

- Duration (hours) of invasive and non-invasive mechanical ventilation (NIV, Optiflow)
- Reintubation
- Assisted ventilation (invasive or non-invasive) at Day 2
- Pneumonia, defined by a radiological infiltrate plus at least 2 criteria: T>38°C; leukocytosis or leukopenia; purulent secretions

Related to Secondary Objective 3 – Infectious Complications Rate:

- Septicemia defined by two positive blood cultures with the same organism within 48h (catheter or peripheral)
- Superficial or deep sternal infection (return to operating room for wound)

Related to Secondary Objective 4 – Pain Assessment:

- VAS (Visual Analog Scale) at Day 1, Day 2, and Day 3
- Total opioid consumption in morphine equivalent mg

Related to Secondary Objective 5:

- Total hospitalization duration in days

Related to Secondary Objective 6:

- Length of stay in intensive care unit and CCU in days

5. SELECTION OF RESEARCH PARTICIPANTS

5.1. Inclusion Criteria

- Over 18 years of age
- Scheduled for non-urgent (>24h) cardiac surgery under CPB
- For women of childbearing age not using effective contraception: negative beta-HCG test
- Having provided written informed consent
- Covered by a social security scheme

5.2. Non-Inclusion Criteria

- Pregnant or breastfeeding women
- Patient under guardianship, curatorship, or judicial protection, or unable to provide consent
- Known allergy or intolerance to naloxegol or any of its excipients or other opioid antagonists
- Severe hepatic impairment (Child-Pugh Class C), history of cirrhosis
- Moderate or severe renal impairment (GFR <60 mL/min by MDRD)
- Known or suspected acute gastrointestinal obstruction
- Conditions likely to alter gastrointestinal wall integrity (severe peptic ulcer, Crohn's disease, diverticulitis, infiltrating tumors of the GI tract or peritoneal metastases)
- History of digestive arteritis (intestinal ischemia or sub-ischemia)
- Cancer with increased risk of gastroduodenal perforation

- Clinically significant blood-brain barrier alteration (primary brain tumor, brain metastases, active multiple sclerosis, advanced Alzheimer's disease, etc.)
- Concomitant use of strong CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole, telithromycin; protease inhibitors: ritonavir, indinavir, saquinavir; grapefruit juice in large quantities)
- Concomitant use of methadone
- Patients regularly taking laxatives
- Patients unable to swallow a whole tablet with a small amount of water
- Patients already included or about to be included in another drug research protocol

5.3. Recruitment Methods

All patients admitted for cardiac surgery under CPB and meeting eligibility criteria will be offered participation in the study. They will be informed at the cardiology consultation before the procedure. Consent will be obtained after ensuring good understanding of the information provided.

6. RESEARCH METHODOLOGY

6.1. Study Type

Prospective, comparative, controlled, randomized, double-blind interventional study (naloxegol tablet or placebo administered by a registered nurse outside the protocol). Physicians, the nurse assessing the primary endpoint, and patients will be blinded to group allocation.

The study compares a group receiving a naloxegol 12.5mg tablet two hours before surgery and 25mg every 24h postoperatively until bowel transit recovery (maximum 5 days) against a control group receiving placebo under the same conditions.

6.2. Study Conduct

6.2.1. In the Cardiology/Cardiac Surgery Ward:

a) Inclusion: Patients will be informed of the protocol by an investigator physician during the cardiology consultation. Clear and transparent information will be provided orally and in writing. Inclusion and non-inclusion criteria will be verified. Informed consent will be obtained after a reflection period deemed sufficient by the patient.

b) Randomization: Patients will be randomized the day before surgery (1:1) into two groups:

- Naloxegol Group: Interventional arm receiving the experimental treatment 'naloxegol'
- Placebo Group: Comparison arm receiving an inert tablet

Randomization will be performed electronically via the eCRF by a nurse 'outside the protocol' who will administer the treatment according to the randomization group.

6.2.2. In the Operating Room:

Standard management of patients for anesthesia and cardiac surgery.

6.2.3. In the ICU and CCU:

- Standard patient management
- Naloxegol Group: administration of a naloxegol 25mg tablet at 24h postoperatively, then every 24h until bowel transit recovery, maximum 5 days
- Placebo Group: administration of an inert tablet at 24h postoperatively, then every 24h until bowel transit recovery, maximum 5 days
- At Day 2 in absence of bowel transit: administration of macrogol until transit recovery
- At Day 4 in absence of bowel transit: administration of sodium picosulfate (Citrafleet)

6.2.4. In the Ward and at Home:

Collection of patient vital status and possible adverse events daily during hospitalization, then at 1 month by telephone call.

6.5. Study Duration

- Planned inclusion duration: 24 months
- Individual patient participation duration: approximately 1 month
- Total study duration: approximately 25 months

6.7. Measures to Reduce or Avoid Bias

6.7.1. Patient Selection:

To avoid selection bias, this study will be proposed to all eligible patients seen at the cardiology consultation.

6.7.2. Randomization:

The treatment number will be revealed via the randomization website to the designated healthcare professional (nurse) for treatment administration. The cardiologist and nurse caring for the patient, who are the sole evaluators, will not know the randomization group, avoiding evaluation bias.

6.7.3. Blinding Procedures:

Pre-randomization will be performed by the sponsor, associating a treatment number (3 digits) with a treatment ('Naloxegol' or 'Placebo'). These numbers will appear on the treatment boxes. Each included patient will receive the treatment provided in the sequential pre-randomization order.

6.8. Stopping Rules for Individual Participants

Any subject included in the study may withdraw consent at any time for any reason without explanation and without affecting the care provided. Early death without bowel transit recovery (absence of primary endpoint) will lead to exclusion from analysis (mITT). These patients will be replaced to avoid loss of statistical power.

7. TREATMENTS ADMINISTERED TO RESEARCH PARTICIPANTS

7.1. Investigational Medicinal Product

Trade Name	MOVENTIG® 12.5mg and 25mg film-coated tablets
INN	Naloxegol
Manufacturer	Piramal Healthcare UK Limited, Morpeth, United Kingdom
MAH	Kyowa Kirin Holdings B.V., Hoofddorp, Netherlands. EU centralized MA: December 8, 2014
Dosing Regimen	12.5mg tablet 2 hours before surgery, then 25mg every 24h after surgery until bowel transit recovery (max 5 days)
Placebo	Inert tablet (Arrow). Round white 300mg tablet. Administered under the same conditions as the active treatment.

7.5. Permitted and Prohibited Concomitant Medications

Concomitant use of naloxegol with strong CYP3A4 inhibitors is contraindicated. Concomitant use with diltiazem or verapamil is not recommended as these increase naloxegol plasma concentration. The following are permitted per standard practice for transit delay management:

- At Day 2 in absence of transit: macrogol administration until transit recovery
- At Day 4 in absence of transit: sodium picosulfate (Citrafleet®)

8. SAFETY EVALUATION

8.1. Definitions

Adverse Event (AE): Any harmful manifestation occurring in a research participant, whether or not related to the research or product.

Serious Adverse Event (SAE): Any AE that causes death, threatens the life of the participant, requires hospitalization or prolongation of hospitalization, causes significant or lasting disability, or results in a congenital abnormality.

Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse effect whose nature, severity, frequency, or evolution does not correspond to reference safety information.

8.4. Protocol-Specific SAEs Requiring Immediate Notification

- Severe symptomatic dehydration (liquid stools >5 times/24h requiring fluid resuscitation >1L)
- Gastrointestinal perforation
- Ogilvie syndrome
- Mesenteric ischemia
- Any severe hemodynamic change not explained by another cause requiring catecholamine support
- Any fatal adverse event, regardless of cause

8.4.2. SAEs Not Requiring Immediate Notification

SAEs related to cardiac surgery (bleeding, shock, myocardial infarction, ventricular arrhythmia, pneumothorax, reoperation) or intensive care (infection, organ failure) will not be considered related to research conduct.

9. STATISTICS

9.1. Statistical Methods

The analysis will proceed in 3 stages:

Descriptive Analysis:

Description of the total population and by group. For categorical variables: absolute and relative frequencies. For normally distributed continuous variables: mean and standard deviation. For non-normal distributions: median and interquartile range.

Inferential Analysis:

Comparisons between the 2 randomized groups will use chi-squared test for categorical variables; Student's t-test for Gaussian continuous variables; Wilcoxon-Mann-Whitney test for non-Gaussian variables. For pain scores over time, a mixed model for repeated measures will be used.

Exploratory Analysis:

Bivariate (correlation coefficients) or multivariate tests (multiple regression, logistic regression) to determine relationships between variables, including the effect of age, sex, and obesity (BMI>30).

9.2. Sample Size Calculation

Primary endpoint: time to bowel transit recovery (quantitative variable). Calculation based on a mean transit recovery time of 48 hours postoperatively. For a 15% reduction (48h to 41h) in the treated group, standard deviation of 20h, alpha risk of 5%, power of 80%, bilateral test: 300 inclusions needed (150 patients per group).

9.3. Significance Level

Bilateral threshold: 0.05

9.7. Analysis Population

Modified intention-to-treat (mITT) population: all randomized patients excluding those who died early without bowel transit recovery (absence of primary endpoint). Each patient will be analyzed in their randomization group. A CONSORT diagram will be provided.

10. DATA ACCESS AND SOURCE DOCUMENTS

10.3. Data Confidentiality

Patient data will be anonymized using inclusion number and initials on research documents. Only coded data will be accessible to the Sponsor. The identity of participants will not be revealed in any report or publication resulting from this study.

The Sponsor declares that data processing will comply with CNIL Reference Methodology MR-001 and GDPR Regulation (EU) 2016/679.

10.4. Archiving

Research documents must be stored by each party for 15 years after the end of the study. No movement or destruction may be carried out without the Sponsor's agreement.

11. QUALITY CONTROL AND ASSURANCE

The Sponsor mandates a Clinical Research Associate (CRA) to conduct monitoring visits verifying: rights, safety, and protection of participants; presence of critical elements for the analysis; accuracy and completeness of reported data; conduct of research in accordance with the protocol, GCPs, and applicable regulations.

12. ETHICAL CONSIDERATIONS

12.1. Declaration of Compliance

The protocol complies with ethical principles established by the World Medical Association (Helsinki Declaration and amendments). It will be conducted in accordance with ICH Good Clinical Practice recommendations.

12.2. Informed Consent

No interventional research may be conducted on a person without their free and informed written consent, obtained after all relevant information has been provided orally and in writing, prior to any protocol procedure. A copy of the signed and dated consent form will be given to the participant.

12.3. Compensation

No compensation is planned for patients in this research.

13. DATA PROCESSING AND DOCUMENT CONSERVATION

13.1. Case Report Form (CRF)

All information required by the protocol will be recorded in an electronic CRF (eCRF) hosted on a central secure server. Data will be collected progressively as obtained by the investigator.

14. FUNDING AND INSURANCE

Study costs are borne by the Sponsor (CMC Ambroise Paré). The Sponsor has subscribed civil liability insurance (Policy No. BARCET19423, Lloyd's, Paris) covering the Sponsor, investigators, and all other parties involved in the research.

15. PUBLICATION RULES

The research will be registered on ClinicalTrials.gov. This study will be the subject of publications in the form of communications and original articles. The order of signatories will be determined by Dr Pierre SQUARA, scientific responsible. CMC Ambroise Paré must be mentioned as the sponsor and financial supporter.

16. REFERENCES

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