STATISTICAL ANALYSIS PLAN

Effects of the peripherally acting μ-opioid receptor antagonist methylnaltrexone on acute pancreatitis severity

Study group
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1. Study Synopsis

Acute pancreatitis is one of the most frequent gastrointestinal discharge diagnoses in Denmark (1) and is associated with complications (20%) and mortality (3%). No targeted pharmacologic treatment exists and thus the management of acute pancreatitis is currently based on supportive therapy and treatment directed against complications such as mono- or multiorgan failure and secondary infections (2).
For patients with acute pancreatitis, pain is the dominant symptom and thus they are exposed to increased amounts of both endo- and exogenous opioids. Opioid administration is known to cause opioid-induced bowel dysfunction primarily by binding μ-opioid receptors in the enteric nervous system (3,4). Thus, opioids promote dysmotility and prolonged gut transit time, which together can cause small intestinal bacterial overgrowth (4). Furthermore, opioids may increase intestinal permeability, resulting in the translocation of bacteria from the gut to the peripancreatic tissue and systemic circulation. Potentially, translocation of bacteria may lead to local and systemic infections, which further may be facilitated by opioid-induced immunosuppression (5,6). Opioids also affect the pancreas directly by decreasing fluid secretion in the pancreatic duct system and increasing the frequency of contractions in the sphincter of Oddi (4,7). This may lead to decreased wash-out of intrapancreatic activated enzymes and thus worsen autodigestion of the tissue and subsequent inflammation of the pancreas. Peripherally acting μ-opioid receptor antagonists (PAMORAs) bind to the μ-opioid receptor with an affinity much stronger than opioid analgesics and thus have the potential to counteract harmful effects of opioids despite high levels of exogenous opioids in patients with pancreatitis.
We hypothesize that treatment with the PAMORA methylnaltrexone will reduce disease severity in patients with acute pancreatitis, compared to placebo. We plan to test this hypothesis by treating patients admitted with acute pancreatitis with methylnaltrexone or placebo in a 1:1 randomization design.

2. Study Objectives, Hypothesis and Outcomes

2.1. Primary Objective and Outcome

The primary objective is to evaluate disease severity in patients with acute pancreatitis during treatment with methylnaltrexone or placebo. The primary outcome will be assessed using the Pancreatitis Activity Scoring System (PASS) score.
PASS is a validated assessment tool for acute pancreatitis based on 5 clinical parameters, which are weighed according to figure 1 (8). It quantitatively evaluates the disease course of acute pancreatitis and has proven useful for monitoring disease severity as well as predicting clinical outcome in patients admitted with this disease (9). Organ failure (i.e. renal, respiratory and cardiovascular) will be assessed according to the Modified Marshall scoring system as defined in the Revised Atlanta criteria (10). Thus, organ failure of the cardiovascular and renal system, is assessed by means of systolic blood pressure and serum creatinine respectively. The ratio between partial pressure of oxygen in arterial blood (PaO_2) and the fraction of inspired oxygen (FiO_2) is used to assess the respiratory system. Not all participants included into this study are expected to have PaO_2 values available. Thus, we will use the ratio between peripheral capillary oxygen saturation (SpO_2) and FiO_2 instead, as previous studies have shown that these two ratios correlate well (11,12).

Pancreatitis activity scoring system

Clinical feature	Weight
Organ failure	100 per system
Intolerance to solid diet	0/40 (N/Y)
Systemic inflammatory response syndrome (SIRS)	25 per criteria
Abdominal pain	(0-10) x 5
Intravenous morphine equivalent dose (mg)	(1/mg) x 5

EXAMPLE: Patient with acute pancreatitis
Kidney failure, tolerant to solid diet, fulfills 1 SIRS criteria,
scores abdominal pain 6, need of 20 mg intravenous morphine
*PASS = 100 + 0 + 25 +(6*5) + (20*5) = **255***

SIRS criteria

1. Body temperature > 38°C or < 36°C
2. Heart rate > 90/min
3. Respiration > 20/min or $PaCO_2$ < 32mmHg
4. White blood cell count > 12.0 x 10_9/L or <4.0 x 10_9/L

EXAMPLE: Patient with acute pancreatitis
Body temperature 37,8°C, Heart rate 120, Respiration 19/min
White blood cell count 18.0 x 10 $_9$/L
*SIRS score = 0 + 1 + 0 + 1 = **2***

Figure 1

We hypothesize that treatment with the PAMORA methylnaltrexone will reduce disease severity as measured by a lower PASS-scores, compared to placebo.

2.2. Secondary Objectives and Outcomes

The secondary objective is to document the effects of methylnaltrexone treatment on several clinical outcomes in patients with acute pancreatitis.
The secondary outcomes are listed below:

- Difference between treatment groups (methylnaltrexone or placebo) in daily PASS-scores during treatment and at 14-day follow-up
- Difference between treatment groups on disease severity assessed using the revised Atlanta criteria (10), where patients are put into one of three categories (mild/moderate/severe)
- Difference between treatment groups on subjective measures of pain intensity and gastrointestinal function assessed using validated questionnaires (13–15) daily during treatment and at 14-day follow-up
- Difference between treatment groups in length of admission and mortality, assessed retrospectively 90 days after admission, using the patients' medical records

2.3. Exploratory Objectives

The exploratory objectives are to examine the effects of methylnaltrexone treatment on the immune system, the gastrointestinal tract, and the pancreas. This is to examine whether treatment with methylnaltrexone may reverse potentially opioid-induced changes to these organs.
The exploratory outcomes are listed below:

- Difference between treatment groups on daily levels of circulating pro- and anti-inflammatory blood markers during treatment and at 14-day follow-up
- Difference between treatment groups in intestinal permeability measured based on the polyethylene glycol (PEG) 400/4000 test (16). Following ingestion of a PEG solution containing 5 g PEG 400 and 5 g PEG 4000 dissolved in 100 ml water, patients will have their urine collected for 24 hours. The small size molecules (PEG 400) traverse the intestinal barrier freely, independent of barrier function loss, whereas the large size molecules (PEG 4000) only cross the intestinal wall and becomes detectable in urine in

case of intestinal barrier function loss. Based on the ratio between the two molecules measured in the urine, we can approximate the intestinal permeability
- Difference between treatment groups on gut transit time assessed using a CT-based radiopaque marker method, where the patients are asked to ingest a capsule containing radiopaque markers 48 hours prior to a CT scan. Based on the location of the markers on the CT-scan, the transit time can be approximated
- Difference between groups on the prevalence of pancreatic complications assessed and quantified using a CT-scan according to the Atlanta criteria (10)

2.4. Descriptive Outcomes

The following variables will be used to describe the study population:
- Age
- Gender
- Time from symptom debut to admission
- Time from symptom debut to randomization
- Aetiology
- Height
- Weight
- BMI

2.5. Specification of endpoints

The primary outcome at the primary endpoint will be analyzed by intention-to-treat (ITT), whereas the secondary endpoints will be per-protocol (PP) analyses. Several factors such as treatment effect of methylnaltrexone and possible side-effects (17) may led to an uneven distribution between excluded patients in the treatment groups (e.g. if methylnaltrexone patients are discharged earlier or discontinue treatment due to side effects). The ITT-analysis will protect against the potential bias of excluding patients unevenly according to which treatment they received. Only if the participant is randomized but never receives treatment, will they be excluded from the ITT-analysis.
The PP-analysis aims to uncover the treatment effect under ideal conditions in terms of treatment duration and follow-up. Furthermore, the PP-analysis is expected to provide mechanistic insights into the role of opioids and opioid antagonism in acute pancreatitis. Participants are included in the PP-analysis, when:

1. > 75 % of the study drug has been given
2. No major protocol deviations have been recorded

The trial is designed as a superiority trial, and we expect to see an effect of treatment after 48 hours of treatment – which is the explanation for choice of primary endpoint. Thus, we expect that the group allocated to the methylnaltrexone treatment, compared to the usual care group, will have:

1. Reduced disease severity (lower PASS-scores, lower prevalence of severe disease)
2. Improved clinical outcomes (lower pain scores, shorter admission lengths, reduced mortality, inflammatory cytokines/intestinal permeability/transit times closer to normal range, reduced prevalence of pancreatic complications)

2.5.1. Primary Endpoint

The primary endpoint will be assessed 48 hours after randomization.

2.5.2. Secondary Endpoints

The secondary and exploratory endpoints are assessed at baseline, daily during treatment and at 14-day follow-up.

3. Study Design

This is a multicenter, investigator-initiated, double-blind, 1:1 randomized, placebo-controlled interventional, parallel-group, superiority trial, that will be conducted at four referral centers for acute pancreatitis in Denmark (Aalborg University Hospital, Odense University Hospital, Copenhagen University Hospital Hvidovre, and Bispebjerg Hospital). The Danish regulations have approved the trial: The North Denmark Region Committee on Health Research Ethics (Identifier: N-20200060) and the Danish Medicines Agency (EudraCT identifier: 2020-002313-18). We plan to prospectively include 90 patients admitted with predicted moderate-to-severe acute pancreatitis. Written informed consent will be obtained from all participants prior to any trial-specific procedures. Patients entering the study, will be randomized 1:1 to receive 5 days of intravenous methylnaltrexone or matching placebo, during admission. While participating in the study, patients will receive standard treatment according to guidelines and no concomitant medication is prohibited. After discharge patients will be invited to complete a 14-day follow. In addition to treatment with PAMORA, patients will undergo a series of examinations daily during treatment and at the 14-day follow-up, according to figure 2.

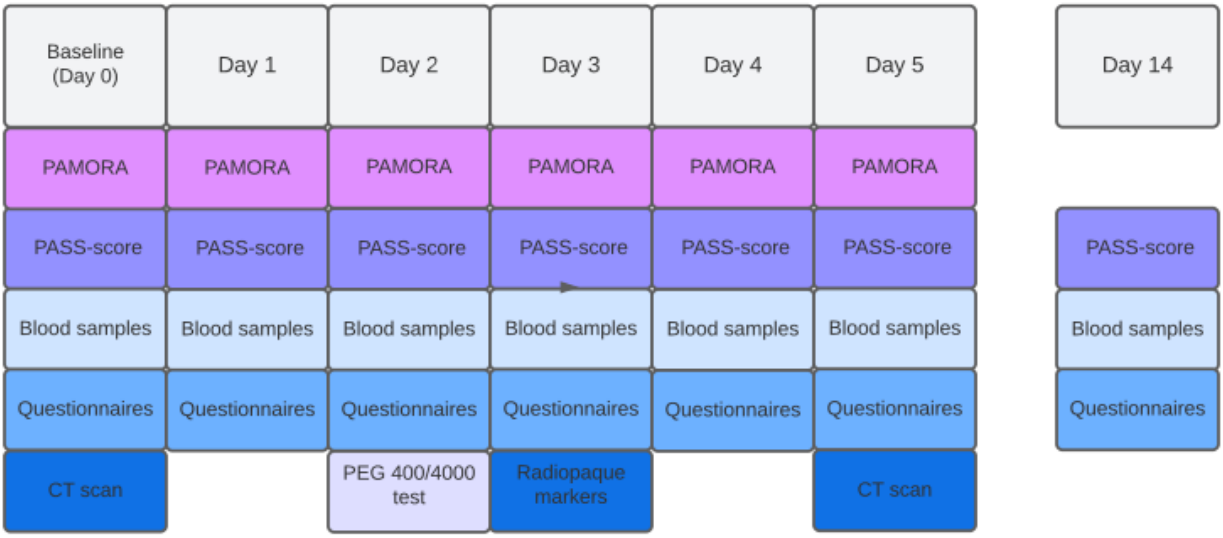

Figure 2

3.1. Sample Size

We calculated that 41 patients per group will be needed to detect a difference in the PASS score of 25 points with a within-group standard deviation of 40 points (9), 80 % power and a 2-sided alfa level of 0.05. Hence, the sample size is set at 45 patients per group to allow for possible dropouts.

3.2. Randomization and Blinding

The Hospital Pharmacy at Herlev Hospital, Denmark, will conduct randomization in random block sizes without stratification (block-randomization) using statistical software approved for

this purpose, e.g. from the website www.randomization.com. Dropouts (treatment with study medication less than 48 hours) will be replaced by new subjects, and a mirror-randomization will be performed.
Labelling will also be performed by the Hospital Pharmacy at Herlev Hospital, according to Annex 13 of the Good Manufacturing Practice guidelines of the International Conference on Harmonization-GCP guidelines and local law. The study medication will be delivered directly to the respective trial sites by the Hospital Pharmacy at Herlev Hospital in vials labelled with the randomization number corresponding to the allocation and the information that it is intended for use in a clinical trial only. Each vial contains 0.6 ml of transparent fluid corresponding to 12 mg methylnaltrexone or matching volume of Ringer's Lactate.
A list of randomization numbers is devised by the Hospital Pharmacy at Herlev Hospital and provided to trial personnel. After inclusion, a randomization number is assigned to the individual trial participant as instructed by the Hospital Pharmacy.

4. Study Population

4.1. Subject Disposition

Patients will be contacted by study personnel upon admission to be informed and potentially included in the study. Participation is complete voluntary, and consent can be revoked, should the participant which to do so. Participants do not receive any economic compensation, but participation will be potentially beneficial for patients receiving active medication and it is expected that this study will produce important knowledge on the treatment of acute pancreatitis for future patients. Furthermore, all patients, regardless of whether they receive active treatment or placebo, may gain new insights and understanding into the pathophysiology of their disease and possible beneficial future treatment.
To identify patients at risk of moderate-to-severe disease, patients must fulfill two or more systemic inflammatory response syndrome (SIRS) criteria within the past 24 hours prior to inclusion. This assumption is based on previous findings that the fulfillment of two or more SIRS criteria is a good predictor of severity in patients with acute pancreatitis (18–20). In- and exclusion criteria are listed below:

Inclusion criteria

- Signed informed consent before any study specific procedures
- Able to read and understand Danish
- Age between 18 and 85 years
- The researcher believes that the participant understands what the study entails, is capable of following instructions, can attend when needed, and is expected to complete the study
- For fertile female participants: negative pregnancy test and use contraception during the study period.
- Within the current hospital admission and prior to inclusion, the patient must fulfill at least two of the following criteria to establish a diagnosis of AP (according to the revised Atlanta criteria (21): i) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); ii) serum amylase activity at least three times greater than the upper limit of normal; and iii) characteristic findings of AP on diagnostic imaging
- Predicted moderate or severe disease based on the fulfillment of 2 or more SIRS criteria

Exclusion criteria

- Definitive chronic pancreatitis according to the M-ANNHEIM criteria

- Known allergy towards study medication
- Known or suspected major stenosis obstruction or perforation of the intestines
- Toxic megacolon
- Known or suspected abdominal cancer (incl. intestine, pancreas and the biliary tree)
- Pre-existing renal insufficiency (defined as habitual estimated glomerular filtration rate (eGFR) below 45 ml/min/1,73m2)
- End-stage renal impairment requiring dialysis prior to inclusion
- Severe pre-existing comorbidities (assessed by investigator upon inclusion)
- Severe non-pancreaticobiliary infections or sepsis caused by non-pancreaticobiliary disease
- Child-Pugh class B or C liver cirrhosis
- Lactating

5. Data handling

Outcome	**Source**	**Data collection rate**	**Datatype**
PASS-score	From the patients' medical records (vital signs, lab results, quantification of need for opioid treatment), self-reported pain intensity and self-reported tolerance to solid foods	Daily during treatment and at 14-day follow-up	Ratio
Disease severity	Stratified as mild/moderate/severe using information about complications and organ failure from medical files	At 14-day follow-up	Ordinal
Subjective measures of pain intensity	Questionnaire: Pain intensity (current + worst/least pain the past 24 hours using NRS), pain interference score (7 parameters, scores 0-10)	Daily during treatment and at 14-day follow-up	Ordinal
Length of admission	Medical records, no. of days	90 days after randomization	Ratio
Mortality	Medical records; deceased y/n	90 days after randomization	Nominal
Circulating levels of pro- and anti-inflammatory cytokines,	Blood samples	Daily during treatment and at 14-day follow-up	Ratio
Intestinal permeability, gut transit time	Urine samples, CT-scans	Once during treatment (day 2-3)	Ratio
Prevalence of pancreatic complications	Stratified according to the revised Atlanta criteria (21) based on CT-scan	On day 5	Ordinal

Table 1

Delegated trial personnel at each trial center will register the collected data in the electronic case report form (eCRF) using the electronic data capture tool REDCap (Research Electronic Data Capture, version 10.6.26) hosted by the organization of The North Denmark Region. REDCap is a secure browser-based software, which meets all regulatory safety requirements (22,23). Data recording will begin when a participant is included and will occur gradually to the end of the trial. A detailed record of any corrections will be kept within REDCap. REDCap also contains features to improve data validation in the form of predefined variable ranges, options to detect that dates are in correct order and warnings if the forms are not sufficiently filled in.
All forms are filled out during (or immediately after) the assessment of a patient. It is possible to export validated data from REDCap to a statistical program (e.g. STATA, R) for further statistical analysis. When data have been entered, reviewed, and verified the data will be locked to prevent editing. Digitalized data are backed up and stored on specific drives at each site under the responsibility of the principal investigators for a minimum of 5 years after the study has ended.

6. Statistical Analysis

For the statistical analysis, the threshold for defining statistical significance will be 0.05. Values will be presented as mean and standard deviation or median and interquartile range depending on normality assessed by the Shapiro-Wilk test. When the data is qualitative, they will be presented as n (%).

6.1. Primary analysis

For the primary analysis of PASS, a repeated measures linear mixed-effects model will be used, and terms for the treatment group, assessment time point, and the interaction of treatment with assessment time point will be included. Baseline PASS scores will be added to the analysis as covariates. In case of statistical significance, a post-hoc Bonferroni corrected t-test will be employed to assess the difference in PASS scores between the groups at 48 hours, assuming normality is also confirmed using the Shapiro-Wilk test. If normality cannot be confirmed, the Mann-Whitney U-test will be used. The difference in PASS scores between the groups 48 hours after randomization is considered the primary efficacy parameter.

6.2. Secondary and exploratory analyses

Secondary and exploratory outcomes will be presented graphically to illustrate trends and potential differences between groups. Thus, outcomes measured repeatedly (PASS-score and levels of pro- and anti-inflammatory cytokines) will be illustrated using trend curves for each treatment group with single time points represented as mean and standard deviation or median and interquartile range, depending on normality. Single time point outcomes will be presented using boxplots depicting the difference between mean and standard deviation or median and interquartile range, depending on normality. Statistical analysis will also be performed for these outcomes according to below.

Repeated measures (e.g. daily PASS-scores, levels of pro- and anti-inflammatory cytokines, subjective measures of pain intensity)
For analysis of repeatedly measured secondary outcomes (daily PASS-scores, daily levels of pro- and anti-inflammatory cytokines), a repeated measures linear mixed-effects model will be used, as described for the primary endpoint. Furthermore, summary statistics and trend curves of PASS scores will be provided for the individual time points.

Single time point outcomes (length of admission, intestinal permeability and gut transit time)
Single time point outcomes (length of admission, measures of gut permeability and transit time) will be compared between groups using the two-sample unpaired t-test, when normality can be confirmed using the Shapiro-Wilk test, or the non-parametric analysis Mann-Whitney U-test when normality cannot be confirmed.

Counted data (disease severity, mortality)
After each patient has been placed in one of three categories (mild/moderate/severe), we will assess whether the prevalence of 'moderate-to-severe' disease is different between the two treatment groups. Thus, a 2 x 2 contingency table will be calculated ('experienced event' (D) being moderate or severe disease, 'did not experience event' (H) being mild disease and the $\chi 2$ test will be employed to test the null hypothesis of no difference between groups.
Mortality between groups (assessed 90 days after randomization) will be analyzed using a 2 x 2 contingency table ('experienced event' (D) being death, 'did not experience event' (H) being survival). As we expect few of our patients to die during the study period, we plan to use Fishers exact test to test the null hypothesis of no difference between groups.

6.3. Major Protocol Deviations

It is expected that a proportion of the patients included into the study, will recover before 5 days have passed and thus be discharged before completing the study protocol. In case of early discharge, data handling of both primary and secondary outcomes be stratified according to table 2:

< 48 hours of treatment	All data collection will be terminated upon discontinuation participant is regarded as dropout.
≥ 48 hours of treatment, but discharge before day 5	Participant will be lost to follow-up on the following outcomes: daily PASS scores, blood samples, vital signs. The participant will be asked to complete questionnaires at home, and they will be offered a follow-up CT scan in an outpatient setting on day 5 (+/- 1 day). Furthermore, they will be invited to participate in the 14-day follow-up and mortality will be registered retrospectively.

Table 2

For the statistical analyses, the Last-Observation-Carried-Forward method will be employed in case of early hospital discharge or other reasons for missing values. We expect most missing values to be a consequence of early discharge (~ recovering early from their disease) and thus the Last-Observation-Carried-Forward method will reflect this by carrying forward a value corresponding to low disease activity after discharge, which we find to be a fair assumption. If this is not the case, e.g. if a lot of missing values are due to severe disease, we will consider using other methods for imputation of missing values.

7. Implementation of Analysis Plan

A monitor will be allocated from the good clinical practice (GCP) unit at Aarhus and Aalborg University Hospitals, and the responsible monitor will contact and visit the principal investigator on a regular basis. The monitor will be authorized to inspect the different study records (CRFs,

source data/documents and other relevant data), provided that the subjects' information is kept confidential in accordance with the data protection agency conditions. It will be the responsibility of the monitor to inspect CRFs regularly throughout the study to ensure compliance and completion of the protocol and that consistent and accurate data is entered in these. If any issues are raised during these monitor visits, the data will be reviewed by the study personnel and compared to source data. After finalization of the study, data will be exported from REDCap in csv-format and all statistical analyses will be performed in R. The statistical analyses will be performed by Ph.D student Cecilie Knoph, supported by supervisor Søren Schou Olesen. All statistical analysis will be performed prior to unblinding.

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