Adjunct Methadone to Decrease the Duration of Mechanical Ventilation in the Medical Intensive Care Unit
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STUDY DESIGN & OBJECTIVE

This is a randomized, double-blind, placebo-controlled trial designed to evaluate the effect of adding methadone to traditional continuous sedation on the duration of mechanical ventilation. The investigators plan to enroll 46 patients.

The primary aim of this study is to compare the duration of mechanical ventilation in patients who receive methadone in addition to traditional continuous sedation (treatment group) and those who receive traditional continuous sedation plus placebo (control group). For each group, the total number of days on the ventilator will be calculated and compared.

BACKGROUND

Short acting opioids such as morphine, hydromorphone and fentanyl are used, typically in combination with a benzodiazepine or propofol for pain management and sedation in ICU. Due to the nature of the pain experienced by this patient population, specifically those requiring mechanical ventilation, fentanyl's short duration of action frequently leads to the need for continuous infusion or frequent bolus dosing. Tolerance and physical dependence develop quickly. Methadone offers unique pharmacokinetic and pharmacodynamic profiles that may provide advantages over these opioids.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

- Mechanically ventilated patients with opioid consumption greater than or equal to 1,200 mcg of fentanyl or equivalent consumption of another opioid per day during the first 48 hours of intubation.

Exclusion Criteria:

- Allergy to methadone
- Admitted for head injury
- Admitted for seizure
- Seizure during admission, prior to enrollment
- Subjects at high risk for developing a prolonged corrected QT (QTc) interval
- Gastric residual volume ≥200 mL
- Suspected obstruction or ileus
- Nausea and vomiting
- Recent abdominal surgery
- Active upper or lower gastrointestinal bleeding
- Active order for no medications by mouth or Total parenteral nutrition (TPN)
- Pregnancy
- Subjects receiving neuromuscular blocker infusions
- Subjects taking antipsychotics at baseline

ADVERSE EFFECTS

- Refer to the package insert, micromedex etc. for details

TREATMENT SCHEDULE

Patients will be randomized in a 1:1 ratio to one of the following Arms:

- Methadone capsules by NG tube/feeding tubes 3 times daily, every 8 hours, for 7 days or until extubation whichever occurs first
- Placebo capsules by NG tube/feeding tubes 3 times daily, every 8 hours, for 7 days or until extubation whichever occurs first

Methadone /Placebo dose calculation: Dosing of the study medication will be based on the doses of opioids they have received prior to initiation of methadone. All opioids received in the previous 24 hours will be converted to morphine equivalents using a conversion table found "Demystifying Opioid Conversion Calculations" and this will be reduced 25% due to lack of complete cross tolerance. The resulting dose will be converted to a methadone dose utilizing a formula described by Ayonrinde et al. The total daily dose calculated will be divided in 3 scheduled doses and will NOT EXCEED 60 mg per day.

ADMINISTRATION

- The blinded capsules will be administered in 3 divided doses every 8 hours by the NG/feeding tubes

STUDY DRUG

- Opaque capsules containing either 5mg of methadone or placebo (lactose) will be prepared by Tom Smoot and team and given to IDS. One bottle of capsules containing methadone 5mg capsules and one bottle of matching placebo (lactose) will be prepared and the expiration date will be set not later than 25 % of the time remaining until the manufacturer's expiration date or 6 months, whichever occurs first.

DRUG ORDER

Initial supply: The instigators will compound the active and placebo capsules and supply them IDS

Resupply: IDS will contact the primary investigator when 50 capsules of each arm remain in the inventory. The investigators will then compound additional capsule to resupply IDS.

DRUG RECEIPT

- Sign invoice and file.

STORAGE

The bulk supply will be stored in the locked drawer in IDS and in central pharmacy pyxis at room temperature (below 25°C) under "Smoot-Methadone study".

SCREENING/ENROLLMENT

PI/Study coordinator will provide IDS with the following information:

1. Patient Name/MRN
2. Signed Drug order in EPIC with pts blinded dose
3. Last signed page of the consent form.
4. Time/date of drug needed

RANDOMIZATION

- Based on the above information provided by the PI, IDS/Central pharmacist will assign the next sequential treatment arm to the patient by referring to the study randomization sheet in the study binder (will be kept in the central binder to ensure the same randomization is not assigned to two different patients)
- Write in date, patient name, MRN on the randomization schedule

DRUG PREPARATION AND DISPENSING

CAUTION: Controlled Substance- schedule II drug, follow appropriate laws and regulations

1. Verify the signed drug order in EPIC and print the label.
2. The order will indicate the patient blinded dose in increments of 5mg
3. Locate the study drug supply per patient randomization, i.e; active or placebo
4. Unit dose each dose per patient randomization, e.g: If patient randomized to the active Methadone arm, at a daily dose of 60mg (divided into 3 doses= 20mg Q8h, so four capsules of 5mg strength will be in each unit dose foil)
5. Label each unit dose aluminum package with EPIC label and package and label enough doses for a 7 day treatment. Also label with "Note Dosage Strength"

stickers. One dose =X # of capsules. Place another EPIC label on the Ziplock bag containing all 21 doses= 7 day supply

6. Label with “Investigational Use Only Label”, “Save and Return All Unused Drug”
7. Deliver the bag to a member of the investigation team and the team will load it into the pyxis machine on the patient floor along with a drug data sheet.
8. The floor nurse will remove one dose at a time from the pyxis machine and administer.
9. If patient discontinues prior to the completion of the 7 day treatment. The remaining doses will be destroyed by Tom Smoot and team and destruction and quantity will be documented on the patient specific log with double signatures meeting control substance destruction requirements.
10. Reconcile each patient medication bag with the number of unit doses prepared, dispensed and then wasted or destroyed. The total should add up at the end.

DO NOT TUBE ANY STUDY MEDICAIONS

LABELS

- EPIC label:
- “Investigational Use Only Label”
- “Save and Return All Unused Drug”

UNBLINDING

- The PI will contact IDS in writing requesting for a patient to be unblinded with the reason for unblinding.
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DRUG ACCOUNTABILITY

1) Complete the Patient Enrollment form
2) Complete the IDS Mater accountability log for active or Placebo capsules
3). Document destruction of each capsule dispensed but not administered on the control substance reconciliation/destruction log along with our log.
4). Document inventory performed on the accountability log after each dispensing from IDS. Double count and signatures required.

PROTOCOL AUTHORIZED PERSONNEL

STUDY PAGER: 146

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