Clinical Pharmacokinetics of Midazolam and Ketamine in Critically Ill Adults on Extracorporeal Membrane Oxygenation

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Introduction and Objective

Introduction

- Extracorporeal Membrane Oxygenation is a form of life support that provides temporary mechanical cardiopulmonary support in patients who cannot provide adequate cardiac output.
- Sedation is achieved through Midazolam, a benzodiazepine, and Ketamine, an NMDA receptor antagonist.
- Use of ECMO in adults has increased recently, more than 400% from 2006-2011 (Sauer, 2015).
- Ex vivo studies show sequestration of Midazolam within the circulation (Tellor, 2015).
- Ketamine shows favorable hemodynamic effects, but use on ECMO adult patients not well described in literature (Tellor, 2015).

Objectives

- Characterize the plasma pharmacokinetic parameters (absorption, distribution, metabolism and elimination) for ketamine and midazolam in critically ill adult patients on ECMO.
- Create a population pharmacokinetic model of critically ill adult patients on ECMO.
- Investigate possible dosing strategies for the purpose of adequate sedation.

Methods

- For the duration of ketamine/midazolam infusion, blood samples will be taken at the just prior, 15 minute, 30 minute, 2 hour, 4 hour, and 6 hour time points and every 12 hour time points thereafter.
- Samples will be taken pre and post-oxygenator every 12 hours.
- Quantification in plasma performed by HPLC/MS-MS.
- Gather information from each patient regarding demographics, vital signs, laboratory parameters and details of ECMO therapy, infusion changes/boluses, concomitant medications.

Study Endpoints

- Pharmacokinetic parameters (volume of distribution and clearance) for ketamine and midazolam and their respective metabolites.
- Pharmacokinetic model describing ketamine, midazolam and their respective metabolites in critically ill adult patients on ECMO.

Results

- In-house assay developed for ketamine, midazolam and their respective metabolites in human plasma using HP/LC-MS.
- Currently have data from 11 subjects:
  - Cardiogenic shock/MI/CHF (5)
  - ARDs/Asthma exacerbation (6)
  - All male
- Example data from subject 105
  - African American male presented with Acute refractory hypercapnic respiratory failure due to asthma exacerbation
  - Placed on venovenous (VV) ECMO for 9 days

Conclusions

Preliminary data shows:

- Plasma concentrations have been successfully measured through an in-house assay for ketamine, midazolam and their respective metabolites.
- Drug concentration discrepancies are seen in pre-oxygenator samples compared to post-oxygenator samples. Discrepancies can be due to any of the following:
  - Sequestration of drug in the ECMO circuit
  - Critically-ill state causing altered kinetics
  - Concomitant drugs or illnesses

Moving forward:

- Continue to compile samples concentration data for remaining subjects.
- Continue to compile clinical data from each subject using electronic medical records (EMR).
- Establish pharmacokinetic parameters.
- Use the clinical data from EMRs to construct a population pharmacokinetic model for adult patients on ECMO.

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References