Morphine Pharmacology in the Hypothermic HIE Neonate

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Neonates + HIE + Hypothermia = Unique Pharmacologic Considerations

PK/PD Variation in Neonates

- Pharmacogenetics
- Size / Body Composition
- Maturation & Development
- Nutrition & Environment
- Hypothermia
- Hypoxic Organ Injury
Morphine in HIE + Hypothermia

- Used for analgesia, sedation and/or shivering
  - Discomfort during cooling, intubation and ventilation
- Frequently Used
  - Commonly part of hypothermia protocols
- Challenging to Use
  - Difficult to assess clinical need in HIE neonate
    - Shivering, Seizures, CNS irritability, Encephalopathy, Opiate CNS Depression?

Morphine Pharmacology

- Morphine metabolized in liver
- Morphine-6-glucuronide (M6G)
  - More potent than morphine and is important component of analgesia and sedation
- Neonates have <10% of adult UGT activity
  - Decreased morphine clearance
  - Less M6G formation
- Metabolite excretion via kidney
  - Accumulation with kidney injury
Elevated Morphine Concentrations in HIE with Hypothermia at Typical Doses

Considered Potentially Toxic Levels

LPCH → Changed standard morphine dose to 0.04 mg/kg IV q6h
Best ‘guess’ from Roka data.
BUT, major limitations to Roka study
- Formal PK analysis not performed
- Morphine metabolites not measured
- No predictive framework to help customize develop dosing strategies

Therefore, further understanding needed!
Clinical PK Study of Morphine in HIE + Hypothermia at LPCH and UCSF (N=20)

- Morphine
  - Clearance ↓50%

- Metabolite
  - Clearance predicted by kidney function (i.e. Serum Cr)

- Large variation in PK variation between neonates (CV% 50%)

Intermittent Dosing = Large Fluctuation In Exposure Between Doses

Unpublished data - Frymoyer A, Van Meurs K, Bonifacio S
Continuous Infusion = More ‘Constant’ Exposure

![Graph showing continuous infusion of morphine at different rates and their effect on concentration over time, with a target range of 10-40 ng/ml.]

Consider Variation Between Neonates
(n=1000 Simulated Neonates per dose)

![Box plot showing variation in morphine concentration among neonates of different weights.]

Target 10-40 ng/ml
Metabolite Accumulates Over Time and Increased with Kidney Injury

Summary – Morphine Use in the Hypothermic HIE Neonate

- Reduced clearance by 50% = Reduced Dose Need
  - Morphine and M6G metabolite (which is active)

- Recommended dose based on clinical PK study at LPCH
  - Loading dose 0.05 mg/kg
  - Then, continuous Infusion 5-10 mcg/kg/h

- Further customize dosing strategy for individual neonate
  - Liver and/or renal impairment?
  - Unique needs of neonate
  - Infusions ≥ 10-15 mcg/kg/h → consider other contributors to clinical symptoms/presentation?