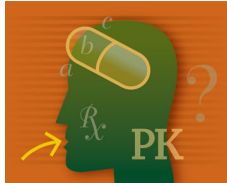


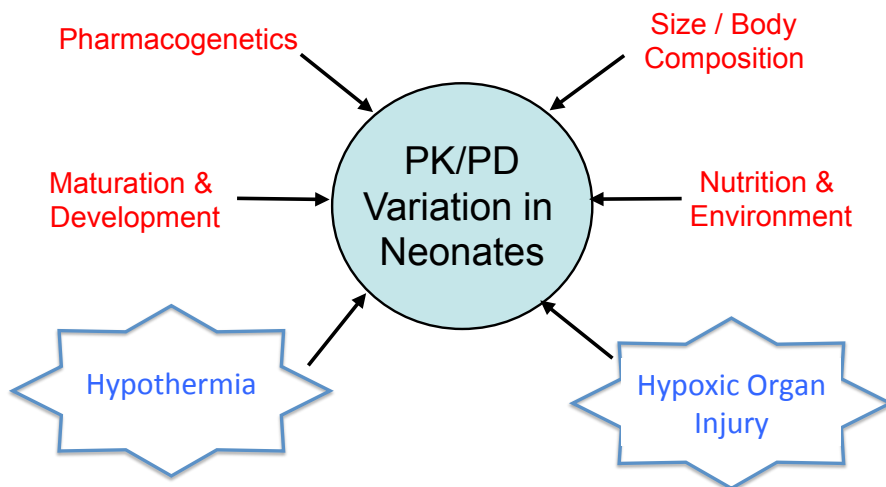
Morphine Pharmacology in the Hypothermic HIE Neonate



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Neonates + HIE + Hypothermia = Unique Pharmacologic Considerations



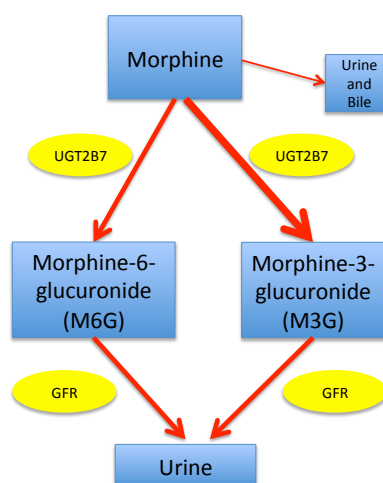
Morphine in HIE + Hypothermia

- 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?

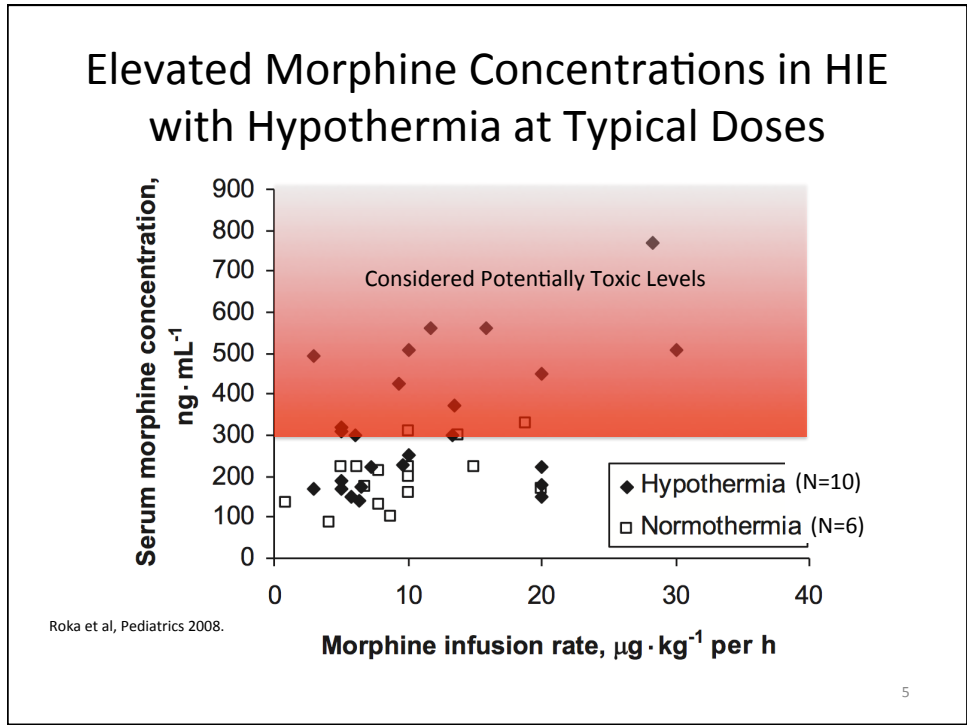
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Morphine Pharmacology

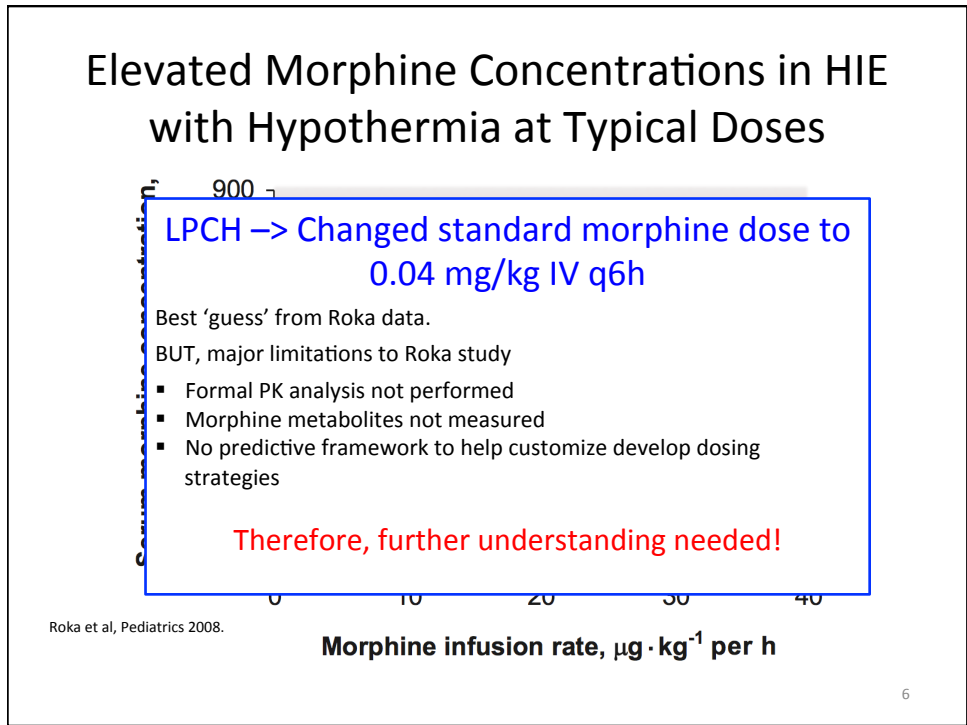
- Morphine metabolized in liver
- Morphine-6-glucuronide (M6G)
 - More potent than morphine and is important component of analgesia and sedation
- Neonates have <10% of adult UGT activity
 - Decreased morphine clearance
 - Less M6G formation
- Metabolite excretion via kidney
 - Accumulation with kidney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



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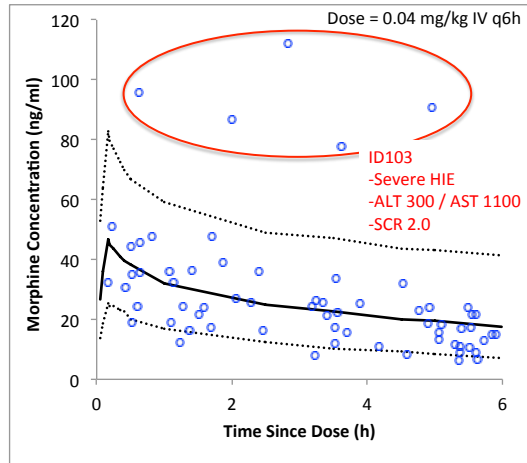
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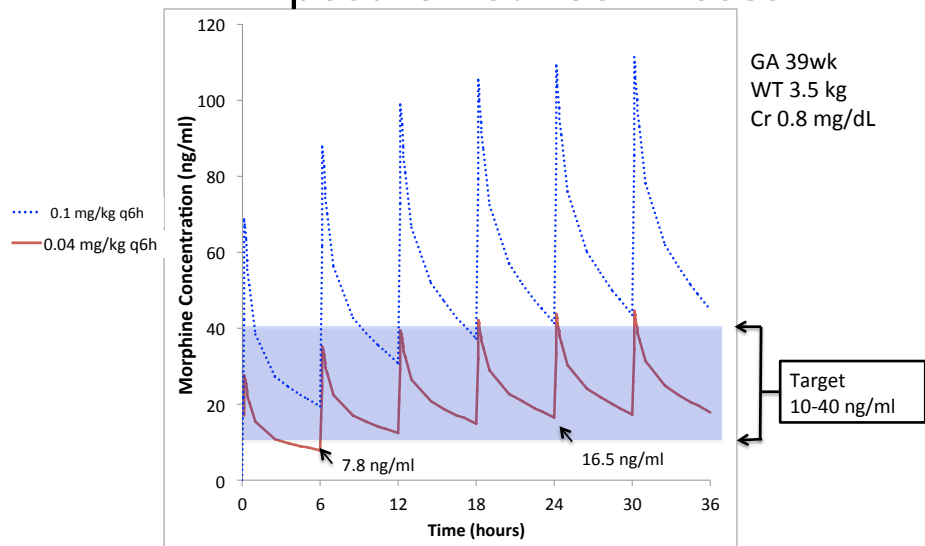
Clinical PK Study of Morphine in HIE + Hypothermia at LPCH and UCSF (N=20)

- Morphine
 - Clearance ↓50%
- Metabolite
 - Clearance predicted by kidney function (i.e. Serum Cr)
- Large variation in PK variation between neonates (CV% 50%)



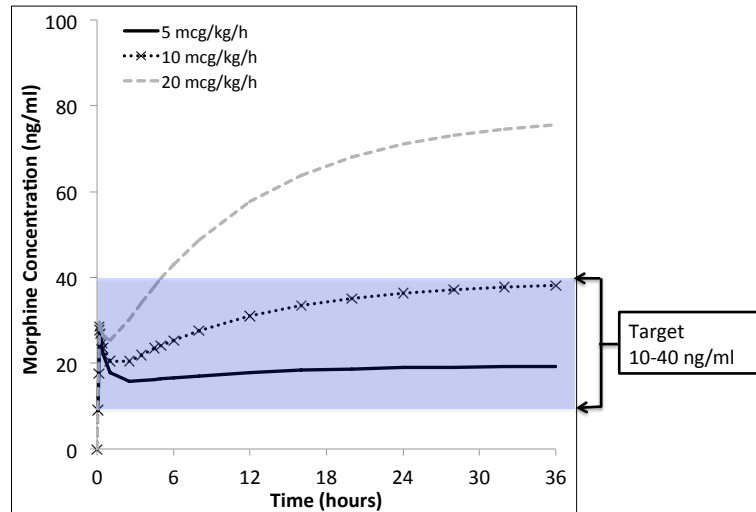
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Intermittent Dosing = Large Fluctuation In Exposure Between Doses

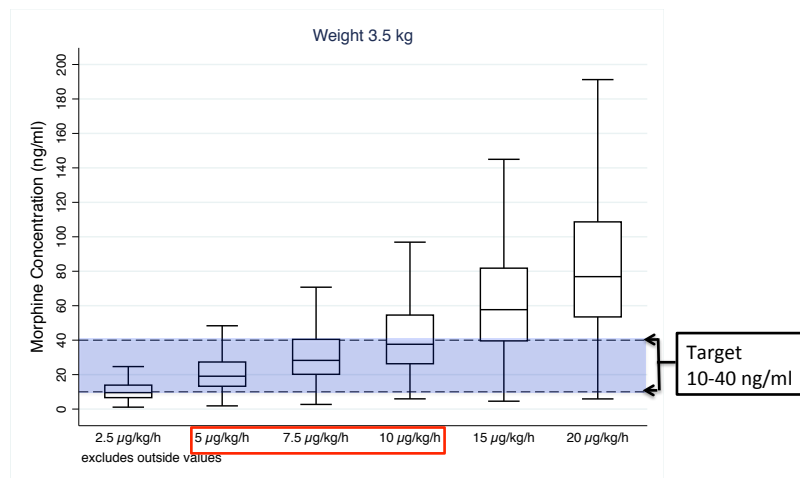


Unpublished data - Frymoyer A, Van Meurs K, Bonifacio S

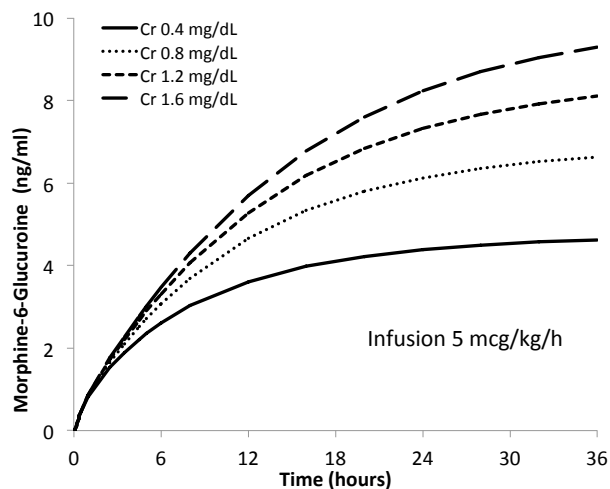
Continuous Infusion = More 'Constant' Exposure



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



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 \rightarrow consider other contributors to clinical symptoms/presentation?