IMPACT OF HIE AND THERAPEUTIC HYPOTHERMIA ON NEONATAL DRUG THERAPY

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OBJECTIVES

- Define basic pharmacokinetic (PK) and pharmacodynamic (PD) principles in neonates
- Describe how HIE and therapeutic hypothermia impact PK and PD in neonates
- Review literature to determine how to optimize pharmacotherapeutic management in infants with HIE and therapeutic hypothermia

DRUG THERAPY

- Goal is to administer a given drug at a given dose to achieve a desired therapeutic effect while minimizing risk of toxicity

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

CHALLENGES TO NEONATAL DRUG THERAPY

- Great variability in drug disposition
  - Maturational development
  - Disease state variability
- Drug formulations
  - Neonatal-specific formulations often lacking
  - Highly concentrated
  - Low infusion rates

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

CHALLENGES IN NEONATAL DRUG DOSING

- Much of the available data for neonatal dosing extrapolated from older children and adults
- Gestational age and weight are most common variables used to determine doses
  - Non-linear relationship between drug metabolism and weight
  - Body surface area (BSA) has been suggested as an alternative but has not been shown to increase accuracy or safety

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

THERAPEUTIC DRUG MONITORING (TDM)

- Powerful tool for improving outcomes associated with medication use
- Can contribute to tailored drug prescribing
- Individualized dosing to maximize benefits while minimizing toxicity
- Supports clinical decision making

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

CRITERIA FOR TDM

- Weak correlation between dose administered and concentration reached
- Wide inter-patient variability in concentration with a given dose
- Narrow therapeutic range
  - Under/over-exposure results in poorer outcome or more toxicity
- Analytical technique sufficiently specific, precise, accurate, and cost effective

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

REASONS TO NOT USE TDM

- Value is limited and there are more convenient methods for assessing effects of dosage based on easily available outcome variables
  - Blood pressure, analgesia, level of sedation
- Broad concentration range before toxicity
- Inability to effectively sample
  - Timing of collection, assay validity
  - Active metabolites complicate assessment

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

PHARMACOKINETICS

- What the body does to the drug
- Describes the movement of drug into, through, and out of the body
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

ASHP Chapter. http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx

PHARMACOKINETIC (PK) PARAMETERS

- Elimination rate
- Half-life
- Clearance
- Volume of distribution
- Peak concentration
- Trough concentration

ASHP Chapter. http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx

DRUG CONCENTRATION

$$\text{concentration} = \frac{\text{amount of drug in body}}{\text{volume in which drug is distributed}}$$

ASHP Chapter. http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx

DRUG VOLUME OF DISTRIBUTION

$$\text{volume of distribution} = \frac{\text{amount of drug}}{\text{concentration}}$$

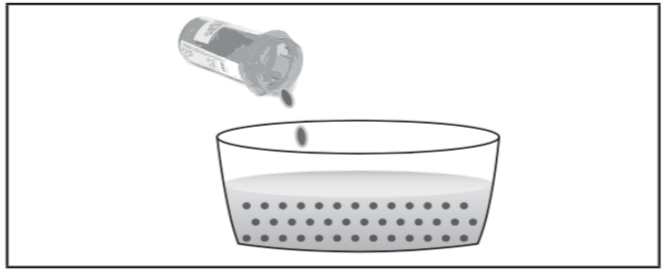

FIGURE 1-20.
The volume of a tank can be determined from the amount of substance added and the resulting concentration.

ASHP Chapter. http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx

PHARMACODYNAMICS (PD)

- What the drug does to the body
  - Receptor binding, post-receptor effects, chemical interactions
- With PK, describes relationship between drug dose and effect
- Interactions can impact drug effects
  - Drug-drug, drug-disease
- Genetic mutations can change binding affinity, alter binding proteins, decrease receptor sensitivity

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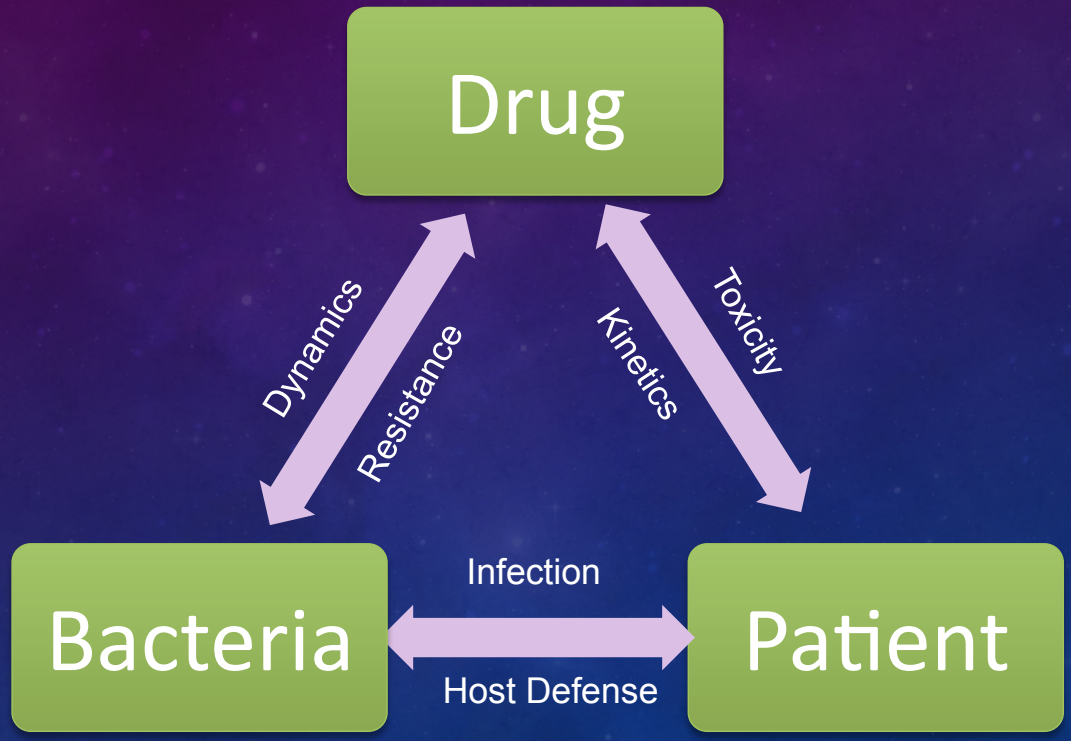
RELATIONSHIP BETWEEN PK-PD



Schentag et al. Pharmacokinetics 3rd Edition. P16-25.

“PHARMACOPHYSIOLOGY”

- The use of a patient’s calculated pharmacokinetic parameters to understand underlying physiology or disease severity

THERMOPHARMACOLOGY

- Study of the influence hypothermia on pharmacokinetic parameters
  - Distribution, metabolism, elimination, and effect of drugs
  - Avoid toxicity or ineffective medication therapy
- Investigation of body temperature on drug disposition, body temperature effect on drug effects, and drug effects upon temperature homeostasis

Van den Broek MPH et al Clin Pharmacokinet 2012

PHYSIOLOGIC EFFECTS OF HIE/ HYPOTHERMIA

- Cardiovascular
- Hemodynamic
- Neurologic
- Respiratory
- Metabolic/endocrine
- Renal
- Fluids/electrolytes
- Gastrointestinal
- Hematologic
- Immunologic

Zanelli S et al. J Perinatol 2011

CARDIOVASCULAR

- Decreased heart rate
  - 14 to 45 bpm during cooling, returns to normal with rewarming
- Increased systemic vascular resistance
  - Vasoconstriction to conserve heat, release of catecholamines and cortisol
    - Unsedated patients
- Decreased cardiac output (CO)
  - 7% for every 1^{o}C drop in core temperature
  - CO at 33^{o}C 67% following rewarming to 37^{o}C
    - No hypotension-decrease in CO matched decrease in oxygen consumption
- Decreased intravascular volume

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METABOLIC/ENDOCRINE

- Decreased metabolic rate
  - 5-7% lower metabolic rate for every 1^{o}C decrease in core temperature
- Decreased glucose utilization
- Decreased insulin release/sensitivity
  - Hyperglycemia associated with worse neurologic outcomes
- Increased catecholamine and cortisol release
  - Stress response in unsedated patients can lead to shivering, increased metabolic rate

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RENAL

- Decreased perfusion and GFR
- Impaired salt and water reabsorption
- Dysregulation of diuresis
  - Decreased urine output secondary to vasoconstriction
  - Increased urine output secondary to cold-induced diuresis

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FLUIDS AND ELECTROLYTES

- Impaired potassium homeostasis
  - Decreased-cellular uptake
  - Increased-rewarming
- Decreased calcium, magnesium, phosphorous

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GASTROINTESTINAL

- Decreased intestinal blood flow
  - Intestinal perfusion may have been impaired
  - No differences in rate of necrotizing enterocolitis when neonates fed low-volume non-nutritive enteral feedings
- Compromised liver perfusion
  - Elevated serum transaminase levels
  - Hypothermia may be protective

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PHARMACOKINETIC CONSIDERATIONS

- Cytochrome P450 function altered during hypothermia
  - Changes in binding pocket conformation, reduced substrate affinity, slowed rate of redox reactions
  - Reduced drug clearance, longer half-life
- Decreased UDPGT activity
- Hemodynamic adaptation to temperature
  - Peripheral vasoconstriction shunting blood away from muscle, skin, fat
  - Smaller volume of distribution
- Reduced cardiac output, increased vascular resistance reduce blood flow to kidneys and liver

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EFFECT OF REWARMING ON PK

- Drugs with large volume of distribution given before start of hypothermia can be sequestered in peripheral tissues
  - Undergo recirculation upon rewarming
  - Higher serum concentrations than expected, greater risk of toxicity
- Prolonged half-life while cooling can undergo increased clearance as enzymatic activity returns to baseline
  - Sub-therapeutic serum concentrations

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MORPHINE

- Commonly used to provide analgesia and sedation during therapeutic hypothermia
- Requires metabolism via UDPGT2B7 to active metabolite morphine-6-glucuronide (M6G)
  - Maturation delayed in normal neonates (<10% adult activity)
  - Yields less active drug, higher concentrations of opioid antagonist
  - Delayed clearance
  - Renal elimination
- M3G is inactive metabolite with pro-convulsant activity
  - Accumulation in renal failure can result in seizures

Frymoyer et al. J Clin Pharmacol 2016

MORPHINE CLEARANCE IN NEONATES WITH HIE

- Prospective, 2-center clinical PK study in 20 neonates with moderate to severe HIE receiving hypothermia (33.5^{o}C)
  - Eligibility for cooling in conjunction with CoolCap criteria
  - Exclusion criteria: need for renal replacement therapy, ECMO, major congenital anomaly
- Morphine continuous infusion
  - Center 1: 20 mcg/kg/hr and decreased to 10 mcg/kg/hr 24 hours after onset of hypothermia treatment
  - Center 2: 40 mcg/kg q6h (standard dose 50-100 mcg/kg q4h in full term neonates without HIE)
  - Doses adjusted based on clinical need, as needed 50-100 mcg/kg boluses for pain/discomfort/shivering

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MORPHINE CLEARANCE IN NEONATES WITH HIE

- 2 sampling periods during study
  - 1st: 12 to 48 hours after start of hypothermia
  - 2nd : 48 to 72 hours after start of hypothermia
- Morphine, M3G, M6G levels evaluated
  - Body weight
  - Renal function
  - Liver function

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MORPHINE CLEARANCE IN NEONATES WITH HIE

- Significant impact on concentrations
  - Birth weight inversely proportional relationship
  - Serum creatinine
- No associated impact
  - Gestational age
  - ALT

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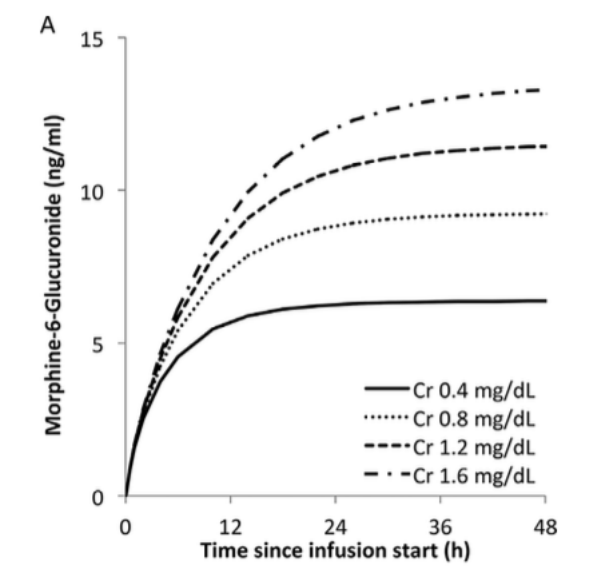
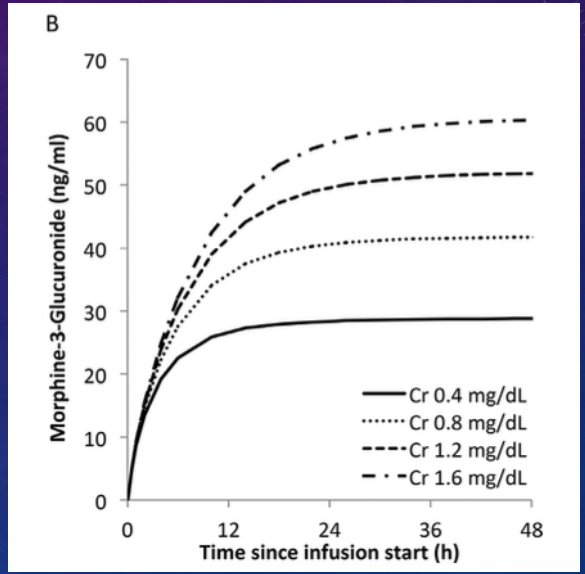
MORPHINE CLEARANCE IN NEONATES WITH HIE





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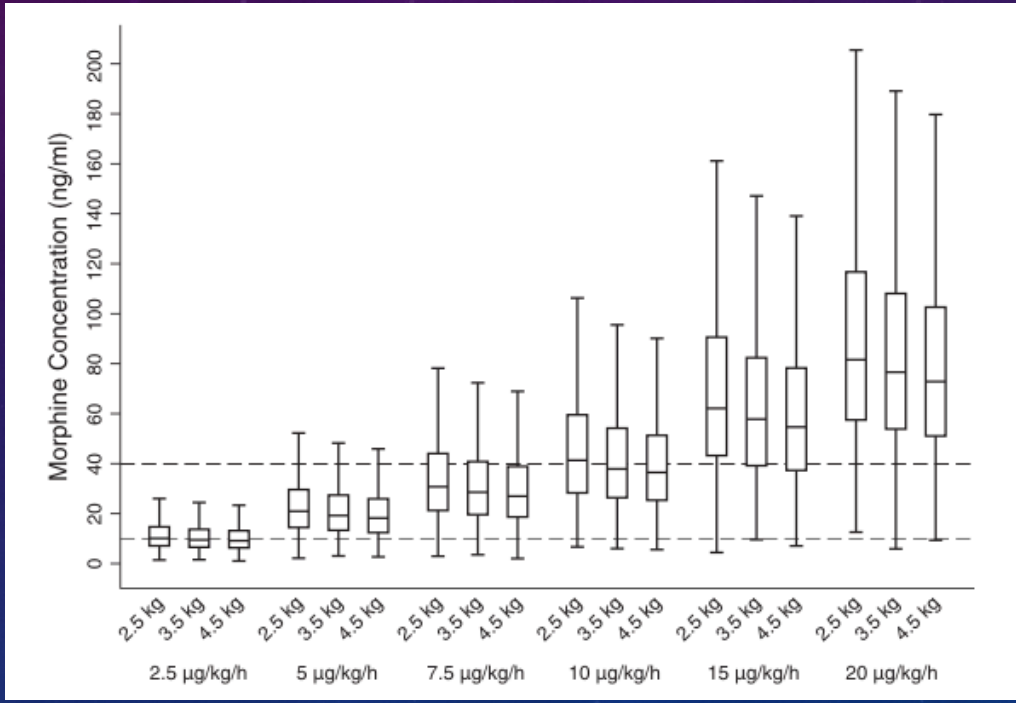
MORPHINE CLEARANCE IN NEONATES WITH HIE



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MORPHINE SUMMARY

- PK effects:
  - Decreased clearance
  - Increased serum concentrations
- Action:
  - Consider starting lower dose
    - Birth weight, SCr
  - Conservative dose titration

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GENTAMICIN IN NEONATES WITH HIE

- Frequently used for presumptive infection/sepsis
- Standard doses for non-HIE term infants frequently results in supra-therapeutic trough concentrations
  - Normothermic: 44%
  - Hypothermic: 36%
- Toxicity: renal, otic

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GENTAMICIN IN NEONATES WITH HIE

- Retrospective chart review of neonates with HIE undergoing therapeutic hypothermia who received gentamicin
- Evaluation of implementation of dosing interval change
  - Dosing: 5 mg/kg q24h or q36h
- Cooling criteria/protocol same between treatment periods
- Gentamicin monitoring:
  - Q24h: trough after 2nd or 3rd dose
  - 36h: peak and torugh

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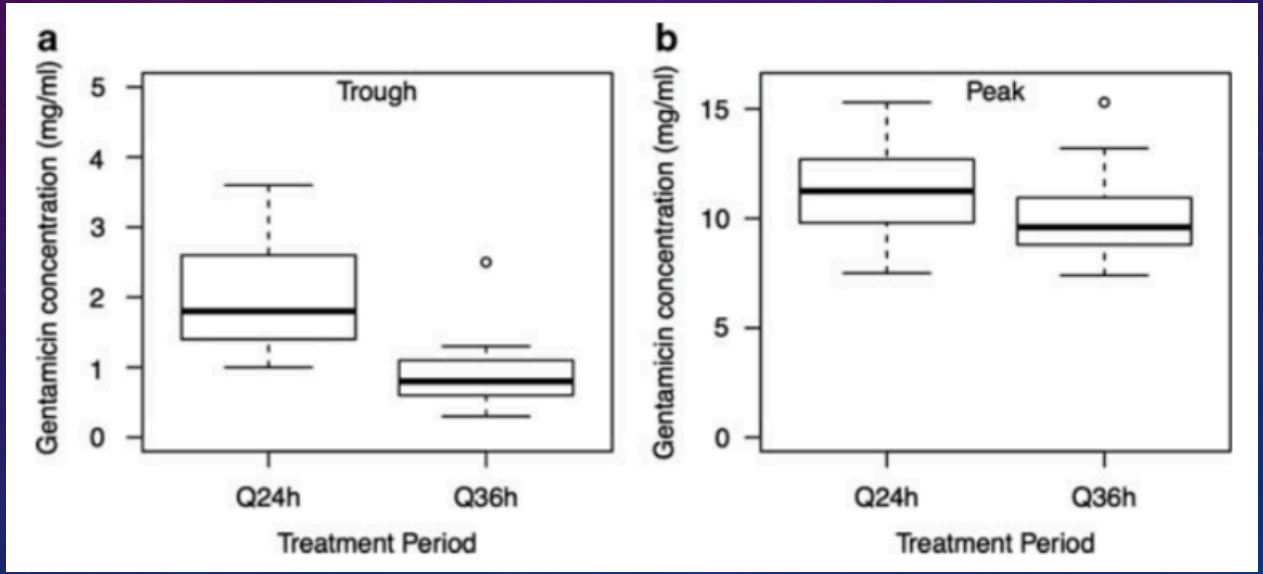
Table 1. Patient demographics

	Q24 h period (n = *29*)		*Q36 h period* (n = *23*)		P-*value*[a]
	Mean ± s.d.	*Min, max*	*Mean ± s.d.*	*Min, max*	
Gestational age (weeks)	39.3 ± 1.9	35.7, 42.3	40.2 ± 1.1	37.6, 41.9	0.048
Birthweight (kg)	3.26 ± 0.58	2.23, 4.83	3.45 ± 0.57	1.87, 4.64	0.3
APGAR					
5 min	3 ± 2	0, 7	4 ± 2	0, 9	0.03
10 min	5 ± 2	0, 9	5 ± 2	0, 10	0.3
First umbilical or arterial pH	7.0 ± 0.2	6.5, 7.3	7.0 ± 0.2	6.7, 7.2	0.6
Base deficit (mmol l^{-1})	−20 ± 8	−4, −35	−15 ± 6	−3, −24	<0.001
Serum creatinine[b] (mg dl^{-1})	1.0 ± 0.3	0.5, 1.5	1.0 ± 0.2	0.6, 1.3	0.6
Assisted ventilation, *n* (%)	24 (83%)	—	17 (74%)	—	0.5
Seizures, *n* (%)	16 (55%)	—	10 (43%)	—	0.6
Dopamine, *n* (%)	18 (62%)	—	12 (52%)	—	0.6
Death before discharge, *n* (%)	6 (21%)	—	0 (0%)	—	0.028

Abbreviations: APGAR, Appearance, Pulse, Grimace, Activity, Respiration; Q24 h, gentamicin 5 mg kg^{-1} every 24 h; Q36 h, gentamicin 5 mg kg^{-1} every 36 h.
[a]*T*-test or Fischer's exact test.
[b]On day of life two; three patients in Q24 h group did not have serum creatinine.

GENTAMICIN IN NEONATES WITH HIE



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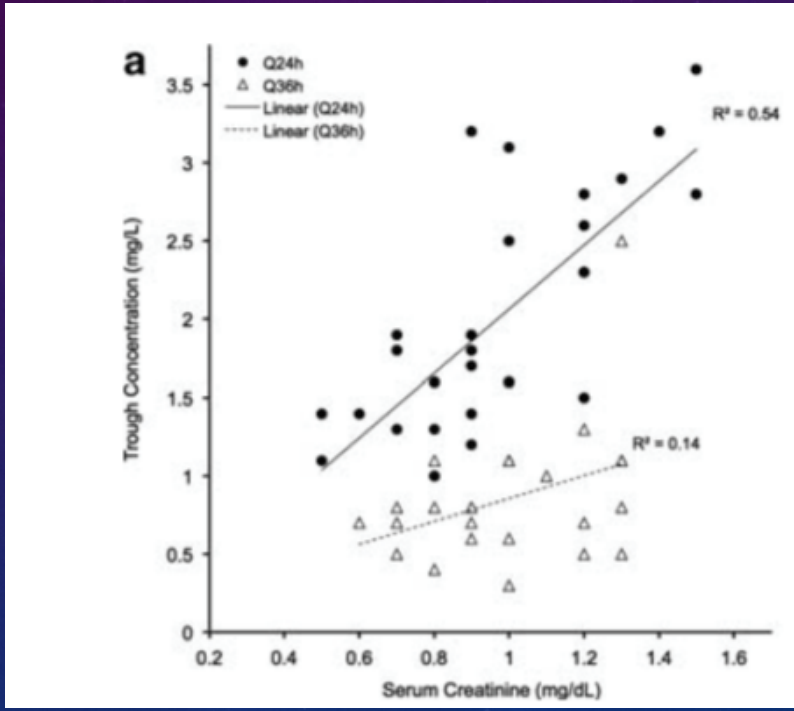
GENTAMICIN IN NEONATES WITH HIE



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GENTAMICIN SUMMARY

- PK effects:
  - Decreased clearance with renal dysfunction
  - Increased serum concentrations (troughs)
- Action:
  - Lower doses versus longer interval

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PHENOBARBITAL IN NEONATES WITH HIE

- HIE is most common cause of seizures in term newborns
- Phenobarbital often first-line anticonvulsant for treatment

Van den Broek MPH et al Clin Pharmacokinet 2012

THERMOPHARMACOLOGICAL APPROACH TO PHENOBARBITAL IN NEWBORNS WITH HYPOTHERMIA

- Neonates ≥ 36 weeks gestation with perinatal asphyxia undergoing moderate hypothermia within 6 hours of birth and continued x 72 hr
- Data obtained from prospective SHIVER study (10 Dutch Level III NICUs)
- Phenobarbital 20 mg/kg divided into 1-2 doses over 20 min per dose if seizures occurred or were suspected during hypothermic phase
  - Maintenance doses not initiated since therapeutic concentrations expected to sustain for several days due to long half-life
  - Subsequent doses only administered upon suspected inefficacy based on clinical symptoms or aEEG recordings
  - Second-line: midazolam or lidocaine

Van den Broek MPH et al Clin Pharmacokinet 2012

THERMOPHARMACOLOGICAL APPROACH TO PHENOBARBITAL IN NEWBORNS WITH HYPOTHERMIA

Table 1 Characteristics of the study population (n = 31)

Characteristic	Value[a]
Sex (n)	
Male	18
Female	13
Gestational age (weeks)	39.9 [36.0–42.1]
Bodyweight (kg)	3.62 [2.15–4.92]
Initial phenobarbital loading dose (mg/kg)	20 [5–40]
Measured plasma concentrations (mg/L) [range]	9.0–37.1
Temperature at start of phenobarbital dosing (°C)	34.6 [32.7–37.0]
Anticonvulsant concomitant medication	
Midazolam add-on therapy (%)	33
Lidocaine add-on therapy (%)	17

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THERMOPHARMACOLOGICAL APPROACH TO PHENOBARBITAL IN NEWBORNS WITH HYPOTHERMIA

- Overall response rate to phenobarbital 66%
- No clinical relevant effect of moderate hypothermia on phenobarbital
  - Clearance is approximately 50% lower in neonates with HIE
- Administration of phenobarbital seems to reduce transition rate from continuous normal voltage to discontinuous normal voltage aEEG background level in hypothermic asphyxiated newborns

PHENOBARBITAL SUMMARY

- PK effects:
  - Decreased hepatic metabolism→ reduced drug clearance
- Action:
  - Monitor serum concentrations
  - Maintenance doses may not need to be started for several days

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FENTANYL

- PK effects-sequestration of drug in periphery
  - Decreased volume of distribution
  - Decreased clearance
  - Increased serum concentrations
- Action:
  - Consider starting lower dose
  - Conservative dose titration
  - Monitoring for increased response during rewarming

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MIDAZOLAM

- PK effects:
  - Decreased clearance
  - Increased volume of distribution
  - Increased serum concentrations
- Action:
  - Start lower dose
  - Conservative titration
  - Monitor for withdrawal or seizures during rewarming

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VECURONIUM

- PK effects:
  - Decreased clearance
- Action:
  - Use lowest effective dose
  - Consider periodic discontinuation to allow for movement

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PHENYTOIN

- PK effects:
  - Decreased clearance
  - Increased serum concentrations
- Action:
  - Lower starting dose
  - Dose adjustments may be needed during rewarming

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TOPIRAMATE

- PK effects:
  - Longer time to max concentrations
  - Decreased clearance
  - Increased serum concentration
- Action:
  - Once daily dosing

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CONCLUSIONS

- Pharmacokinetics may be altered by the presence of HIE and therapeutic hypothermia
  - Effect may yield clinically significant risk of toxicity or under-treatment
  - Effect may be clinically irrelevant
- Since hypothermia is now standard of care for moderate-severe HIE, hard to determine if PK changes are from HIE or hypothermia
- Individualized pharmacotherapeutic plans may be necessary to optimize response and minimize risk of toxicity

QUESTIONS