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

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

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

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

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

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

PHARMACOKINETICS

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

PHARMACOKINETIC (PK) PARAMETERS

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

DRUG CONCENTRATION

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

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
RELATIONSHIP BETWEEN PK-PD

Drug

Bacteria

Patient

Dynamics
Resistance
Toxicity

Infection
Host Defense

“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

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°C drop in core temperature
  - CO at 33°C 67% following rewarming to 37°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°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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RENAI

- 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
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

MORPHINE CLEARANCE IN NEONATES WITH HIE

• Prospective, 2-center clinical PK study in 20 neonates with moderate to severe HIE receiving hypothermia (33.5°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

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

MORPHINE CLEARANCE IN NEONATES WITH HIE

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

MORPHINE CLEARANCE IN NEONATES WITH HIE

MORPHINE CLEARANCE IN NEONATES WITH HIE

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

Frymoyer et al. J Perinatol 2013
**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 2\(^{nd}\) or 3\(^{rd}\) dose
  - 36h: peak and trough

Frymoyer et al. J Perinatol 2013
<table>
<thead>
<tr>
<th></th>
<th>Q24 h period (n = 29)</th>
<th></th>
<th>Q36 h period (n = 23)</th>
<th></th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± s.d.</td>
<td>Min, max</td>
<td>Mean ± s.d.</td>
<td>Min, max</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.3 ± 1.9</td>
<td>35.7, 42.3</td>
<td>40.2 ± 1.1</td>
<td>37.6, 41.9</td>
<td>0.048</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>3.26 ± 0.58</td>
<td>2.23, 4.83</td>
<td>3.45 ± 0.57</td>
<td>1.87, 4.64</td>
<td>0.3</td>
</tr>
<tr>
<td>APGAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>3 ± 2</td>
<td>0, 7</td>
<td>4 ± 2</td>
<td>0, 9</td>
<td>0.03</td>
</tr>
<tr>
<td>10 min</td>
<td>5 ± 2</td>
<td>0, 9</td>
<td>5 ± 2</td>
<td>0, 10</td>
<td>0.3</td>
</tr>
<tr>
<td>First umbilical or arterial pH</td>
<td>7.0 ± 0.2</td>
<td>6.5, 7.3</td>
<td>7.0 ± 0.2</td>
<td>6.7, 7.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Base deficit (mmol L⁻¹)</td>
<td>−20 ± 8</td>
<td>−4, −35</td>
<td>−15 ± 6</td>
<td>−3, −24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinineb (mg dl⁻¹)</td>
<td>1.0 ± 0.3</td>
<td>0.5, 1.5</td>
<td>1.0 ± 0.2</td>
<td>0.6, 1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Assisted ventilation, n (%)</td>
<td>24 (83%)</td>
<td>—</td>
<td>17 (74%)</td>
<td>—</td>
<td>0.5</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>16 (55%)</td>
<td>—</td>
<td>10 (43%)</td>
<td>—</td>
<td>0.6</td>
</tr>
<tr>
<td>Dopamine, n (%)</td>
<td>18 (62%)</td>
<td>—</td>
<td>12 (52%)</td>
<td>—</td>
<td>0.6</td>
</tr>
<tr>
<td>Death before discharge, n (%)</td>
<td>6 (21%)</td>
<td>—</td>
<td>0 (0%)</td>
<td>—</td>
<td>0.028</td>
</tr>
</tbody>
</table>

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.

bOn day of life two; three patients in Q24 h group did not have serum creatinine.
GENTAMICIN IN NEONATES WITH HIE

Frymoyer et al. J Perinatol 2013
GENTAMICIN IN NEONATES WITH HIE

Frymoyer et al. J Perinatol 2013
GENTAMICIN SUMMARY

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

Zanelli S et al. J Perinatol 2011
PHENOBARBITAL IN NEONATES WITH HIE

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

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

THERMOPHARMACOLOGICAL APPROACH TO PHENOBARBITAL IN NEWBORNS WITH HYPOTHERMIA

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

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

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

Zanelli S et al. J Perinatol 2011
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

Zanelli S et al. J Perinatol 2011
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