Pharmacology in the Newborn with HIE

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Disclosures

- Financial
  - No relevant financial relationships to disclose

- FDA
  - Nothing to disclose
Objectives

- Discuss the medications involved in the care of an infant with Hypoxic-Ischemic Encephalopathy
- Define Hypoxic-Ischemic Encephalopathy or HIE
- Describe the mechanisms of the protection of hypothermia
Maternal History

- Mother is a 28 y.o., gravida 1, African-American woman
- Blood type: A negative
- Received early and regular prenatal care
- Delivery was planned in her home town at a community hospital
Delivery History

- Mother presented to the community hospital at 39 weeks gestation in labor
- Rapid second stage dilatation
- SROM with MSAF
- Episodes of fetal bradycardia with recovery
- Vaginal delivery assisted by vacuum extraction
- Tight nuchal cord x 1, with the cord tearing during the attempt to remove the cord from the neck and deliver the baby
Delivery (continued)

- Moderate blood loss with the clamping and cutting of the cord
- Infant was rapidly placed in a warmer, apneic, without spontaneous activity, HR < 100 bpm
- The nurse suctioned out the mouth and a physician immediately intubated the infant with a 4.0 ETT and suctioned ETT receiving meconium below the cords. A second intubation received no meconium, so the infant was reintubated and the ETT was secured at 9.5 cm at the lip.
The infant continued to be apneic and the HR was now 40 bpm. Positive pressure ventilation was provided and chest compressions were begun with the heart rate rising to about 50 bpm. The infant was given a dose of epinephrine ET while equipment was prepared for umbilical line insertion for future doses if needed. With the epinephrine and continued PPV, the infant’s heart rate increased to 70 bpm and very slowly continued to increase.
Epinephrine

- **Therapeutic Category**: Adrenergic Agonist Agent

- **Uses**: Acute cardiovascular collapse/cardiac arrest. Short-term use for systemic hypotension. May also be used for treatment of bronchospasm.

Epinephrine (continued)

- **Administration:**

  Resuscitation and Severe Bradycardia: 0.1 to 0.3 ml/kg of 1:10,000 concentration, IV push = 0.01-0.03 mg/kg (10 to 30 mcg/kg).

  May be given ET using higher doses up to 0.1 mg/kg (100 mcg/kg) immediately followed by NS.

  IV continuous infusion: Start at 0.1 mcg/kg per minute and adjust to desired response.

Epinephrine (continued)

- **Adverse Effects/Precautions:**
  Continuous infusions may cause hyperglycemia, tachycardia, and elevations in serum lactate. Cardiac arrhythmia are possible. Renal vascular ischemia at higher doses.

  Bolus doses maybe associated with severe hypertension and intracranial hemorrhage. Myocardial oxygen requirements may be increased.

Epinephrine (continued)

- **Mechanism of Action:** stimulates $\alpha_{1}-, \beta_{1}-, \beta_{2}$-adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation, and dilation of skeletal muscle vasculature.

- **Pharmacodynamics:**
  - Onset of action: 5 min.
  - Duration: < 1 hour
  - Onset of bronchodilation:
    - Inhalation: within 1 hour
    - SubQ: within 5-10 min.

- **Pharmacokinetics:** no neonatal info available.

Delivery continued

- Very little respiratory effort was noted, only an occasional gasp. The infant remained extremely pale, and limp, but was becoming pinker. Apgars were 1 at 1 minute and 3 at five minutes and 5 at ten minutes. The pH on the venous cord gas was 6.95.

- The radiant warmer was turned off to provide passive hypothermia for this asphyxiated infant.

- The decision was made to give the infant a normal saline bolus due to probable hypovolemia. A low lying UVC was inserted for this.
Normal Saline

- **Use:** Poor response to effective ventilation, chest compressions and epinephrine, pale color, delayed capillary refill, weak pulses, history of condition associated with fetal blood loss.

- **Dose and Administration:**
  10 ml/kg IV, may repeat
  Best route at delivery is umbilical vein or intraosseous.
  Should be given by steady infusion over 5 to 10 minutes.

Normal Saline  (continued)

- **Dosage and administration continued:** Administer slowly in preterm infants, as they are especially susceptible to intracranial hemorrhage with rapid volume administration.

- **Mechanism of Action:** volume expansion for hypovolemia due to causes such as placenta previa and abruption, twin-to-twin transfusion, blood loss from the umbilical cord, or a significant fetal-maternal hemorrhage without obvious blood loss.

Asphyxia according to the AAP/ACOG Criteria

- Profound metabolic or mixed acidemia (pH <7.00) in an umbilical artery blood sample, if obtained
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae
  - Seizure, coma, hyptonia
- Multiple organ involvement
The infant’s heart rate was steady between 80-90 bpm with irregular respirations and occasional quivering movement of the extremities.

The transport team from the Regional Hospital arrived and assessed the infant. Umbilical lines were appropriately placed, blood work drawn, antibiotics started (Ampicillin and Gentamicin) and the infant was placed in a non-warmed transport isolette on a ventilator for transport to the NICU.
Ampicillin

- **Therapeutic Category:** Antibiotic

- **Use:** A broad-spectrum antibiotic used in the treatment of susceptible bacterial infections caused by Group B streptococcus, pneumococci, Listeria monocytogenes, enterococci, and susceptible E Coli species.


Ampicillin (continued)

Administration:
- **Dose:** 25 to 50 mg/kg per dose.
- **Route:** IV slow push or IM
- **Dosing for meningitis and severe group B streptococcal sepsis:** 100 mg/kg/dose

Dosing Interval Chart

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29</td>
<td>0 to 28</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>8</td>
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<tr>
<td>30 to 36</td>
<td>0 to 14</td>
<td>12</td>
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<td></td>
<td>&gt;14</td>
<td>8</td>
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<tr>
<td>37 to 44</td>
<td>0 to 7</td>
<td>12</td>
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<td></td>
<td>&gt;7</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>ALL</td>
<td>6</td>
</tr>
</tbody>
</table>

Ampicillin (continued)

- **Adverse Reactions/ Precautions:**
  - Central Nervous System: CNS excitation or seizure activity with large doses
  - Hypersensitivity/Dermatologic: rash – rare in infants
  - Gastrointestinal: Diarrhea (20%), vomiting, glossitis, pseudo membranous enterocolitis, oral candidiasis
  - Hematologic: Eosinophilia, hemolytic anemia, thrombocytopenia, neutropenia, prolongation of bleeding time
  - Renal: Interstitial nephritis


Ampicillin (continued)

- **Mechanism of Action:** Ampicillin binds to one or more penicillin-binding proteins during the active multiplication phase of bacterial cell wall synthesis, interfering with the synthesis and causing cell wall death. ¹

- **Pharmacokinetics:**
  - Half life:
    - Neonates < 7 days of age: 4 hours
  - Clearance: Primarily renal and inversely related to postnatal age. ²

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Gentamicin

- **Therapeutic Category:** Antibiotic, Aminoglycoside

- **Use:** Used in combination with β-lactam antibiotics as empiric therapy for sepsis in newborns. Treatment of bacterial infections caused by aerobic gram-negative bacilli such as Pseudomonas, E.Coli, Klebsiella, Proteus, Seratia, and gram-positive staphylococcus. Also used for the treatment of bone, CNS, respiratory tract, skin and soft tissue infections.

Gentamicin (continued)

- **Administration:**
  - IV- on syringe pump over 30 minutes.
  - IM- associated with variable absorption

- **Dosing Chart and Intervals—>**
  *or significant asphyxia, PDA, or treatment with indomethacin

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Post-natal (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hours)</th>
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<tbody>
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<td>&lt; 29*</td>
<td>0 to 7</td>
<td>5</td>
<td>48</td>
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<tr>
<td></td>
<td>8 to 28</td>
<td>4</td>
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<td>4</td>
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<td>30 to 34</td>
<td>0 to 7</td>
<td>4.5</td>
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<td>&gt; 8</td>
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<tr>
<td>&gt;35</td>
<td>ALL</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

Gentamicin (continued)

- **Time to peak serum concentration:**
  IM: Within 30-90 minutes
  IV: 30 minutes after 30-minute infusion

- **Elimination:** Clearance is directly related to renal function; eliminated almost completely by glomerular filtration of unchanged drug with excretion into urine.

- **Clearance:**
  Neonates: 0.045 + 0.01L/hour/kg

Gentamicin (continued)

- If treating for more than 48 hours, measure serum concentrations.
- The peak concentration should be obtained 30 minutes after the end of the infusion.
- The trough concentration should be obtained just prior to the next dose.
- Therapeutic serum concentrations:
  - Peak: 5 to 12 mcg/ml
  - Trough: 0.5 to 1 mcg/ml

Gentamicin (continued)

- **Mechanism of Action:** Gentamicin binds to 30S and 50S ribosomal subunits, which inhibits cellular initiation of bacterial protein synthesis and results in a defective bacterial cell membrane.

- **Pharmacokinetics:**
  Distribution: increased in neonates with fever, edema, ascites, fluid overload. Decreased in patients with dehydration:
  \[ V_d \text{ Neonates: } 0.45 \pm 0.1 \text{ L/kg} \]
  Protein binding: < 30%
  Half-life:
  Neonates: < 1 week: 3-11.5 hours
  1 week to 1 month: 3-6 hours

Gentamicin (continued)

- **Adverse Reactions/Precautions:**
- **Black Box Warning:** Aminoglycoside therapy has been associated with possible neurotoxicity, ototoxicity, and nephrotoxicity.

Neuromuscular & Skeletal: neuromuscular blockade
Otic: damage is usually irreversible.

Renal: Risk of toxicity with impaired renal function, dehydration, high dosages, or prolonged therapy.

Transport Care

- Helicopter transport was not possible, so the infant was transported 1 ½ hours by ground.

- About one hour into the transport, the infant began to have seizures including smacking movements of the mouth, and cycling of the extremities. A loading dose of Phenobarbital was given.
Phenobarbital

○ **Therapeutic Category:** Anticonvulsant, Barbiturate; Hypnotic; Sedative

○ **Uses:** Management of generalized tonic-clonic and partial seizures; neonatal seizures. May improve outcome in severely asphyxiated infants. Neonatal abstinence syndrome in nonopiate- or polydrug-exposed infants. May lower bilirubin in chronic cholestasis.

Phenobarbital (continued)

- **Dose and Administration:**
  - Anticonvulsant: Loading dose of 20 mg/kg given IV over 10 to 15 minutes. For refractory seizures an additional 5 mg/kg may be given up to a total of 40 mg/kg.
  - Maintenance: 3 to 4 mg/kg per day beginning 12 to 24 hours after loading dose.
  - Neonatal Abstinence Syndrome:
    - Load of 16 mg/kg PO on day 1.
    - Maintenance of 1-4 mg/kg/dose PO q 12 hours.
    - Based on abstinence scoring.

Phenobarbital (continued)

- **Adverse Reactions:**
  Cardiovascular: hypotension, circulatory collapse, bradycardia
  Central Nervous System: sedation at serum concentrations above 40 mcg/ml.
  Respiratory: depression at concentrations above 60 mcg/ml
  Irritating to veins.

- **Mechanism of Action:** Limits the spread of seizure activity, possibly by increasing inhibitory neurotransmission. Depresses the CNS activity by binding to the barbiturate site at the GABA-receptor complex. Depresses the reticular activating system.


Phenobarbital (continued)

- **Pharmacodynamics:**
  - Onset of action:
    - Oral: within 20-60 minutes
    - IV: within 5 minutes
  - Maximum Effect: IV within 30 minutes
  - Duration:
    - Oral: 6-10 hours
    - IV: 4-10 hours

Phenobarbital (continued)

- **Pharmacokinetics:**
  - Distribution $V_d$: 0.8-1 L/kg
  - Protein binding: 35-50%
  - Metabolism: in the liver by hydroxylation and glucuronide conjugation
  - Half-life: 45-500 hours
  - Time to peak concentration: oral 1-6 hours
  - Elimination: 20-50% excreted unchanged in urine.

NICU Admission

- Upon admission to the NICU, the infant was noted to be lethargic, with decreased muscle tone. He had increased tendon reflexes and overactive dolls-eye reflex, a weak suck and incomplete moro. Frequent seizure activity continued so a standard EEG was obtained documenting the seizure activity and a second anticonvulsant, phenytoin was added.
Phenytoin

- **Therapeutic Category:** antiarrhythmic, anticonvulsant
- **Uses:** anticonvulsant used to treat seizures that are refractory to phenobarbital.
- **Dosage and administration:**
  - Loading dose: 15 to 20 mg/kg IV infusion over 30 minutes.
  - Maintenance dose: 4 to 8 mg/kg q 24 hours IV slow push or PO.

Phenytoin (continued)

- **Dosage and administration con’t:**
  (up to 8 mg/kg per dose q 8-12 hours after 1 week of age)
  Maximum infusion rate 0.5 mg/kg/min. Flush IV with saline before and after.

**Warning:** Phenytoin is highly unstable in any IV solution. Avoid use in central lines due to precipitation. IM not acceptable as drug crystallizes in the muscle.

Phenytoin (continued)

- **Adverse Reactions:**
  
  Extravasation causes tissue inflammation and necrosis.

  High serum concentrations are associated with seizures.

  Hypersensitivity has been reported in infants.

  Toxicity includes: cardiac arrhythmias, hypotension, gingivitis, nystagmus, rickets, hyperglycemia and hypoinsulinemia.

Phenytoin (continued)

- **Mechanism of Action:** Stabilizes neuronal membranes and decreases seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses.

- **Pharmacokinetics:**
  - Distribution: $V_d$
  - Preterm: 1-1.2 L/kg
  - Full term: 0.8-0.9 L/kg

Phenytoin (continued)

- **Pharmacokinetics:**
  Protein binding: Adults 90-95%, decreased protein binding in neonates (up to 20% free)
  
  Metabolism: is dose-dependent, half-life is dependent on serum concentration.
  
  Elimination: < 5% excreted unchanged in urine

NICU Admission

- Lorazepam or fosphenytoin would be other anticonvulsant options. The infant met criteria for Stage 2-Moderate Encephalopathy (Hypoxic Ischemic Encephalopathy) and met the hospital criteria for therapeutic body cooling. The infant was placed on a cooling blanket with the radiant warmer turned off. An esophageal probe was inserted to monitor the infant’s temperature. The infant was on a ventilator, a cardiorespiratory monitor, pulse oximetry, and an aEEG machine.
aEEG

- During the time the infant is on whole body cooling, a continuous EEG or aEEG may be in place.

- An aEEG or amplitude-integrated EEG, or Cerebral Function Monitor (CFM), is a device that measures background electrocortical activity in the brain.

- Uses a single lead, consisting of three wires placed over the biparietal or frontal region of the head

- Indicates the generalized level of electrical activity that is occurring across the brain

aEEG (continued)

- Research has shown the aEEG to be a sensitive tool for predicting severity of HIE if applied in the first 6-12 hours following perinatal asphyxia.

- Also valuable detection tool for neonates experiencing clinical or subclinical seizures.

Indications for an aEEG

- Hypoxic ischemic encephalopathy
- Seizures
- Significant neurological disorders
- Post cardiac arrest
- Inborn error of metabolism
- Neonatal abstinence syndrome

Pitfalls:
The aEEG requires lead stabilization to decrease or eliminate artifact caused by HFOV.

Lorazepam

- **Therapeutic Category:** Antianxiety agent, anticonvulsant, benzodiazepine.

- **Uses:** Acute management of seizures refractory to conventional therapy.

- **Dosage and Administration:**
  0.05 – 0.1 mg/kg per dose IV slow push. Repeat dose based on clinical response.

- **Adverse Effects:**
  Respiratory Depression. Some preterm infants have had rhythmic myoclonic jerking when receiving lorazepam for sedation.


Lorazepam (continued)

- **Mechanism of Action:** Depresses all levels of the CNS including the limbic and reticular formation by binding to the benzodiazepine site on the GABA receptor complex.

- **Pharmacodynamics:**
  
  Onset of action:
  Oral: within 60 minutes
  IM: 30-60 minutes
  IV: 15-30 minutes

  Duration: 8-12 hours

Lorazepam (continued)

- **Pharmacokinetics:**
  - Distribution: \( V_d = 0.76 \text{ L/kg} \)
  - Protein binding: 85%
  - Metabolism: primarily by glucuronide conjugation in the liver
  - Half-life:
    - Full term neonates: 40.2 hours; range 18-73 hours
  - Elimination: in urine primarily as glucuronide conjugate

Fosphenytoin

- **Therapeutic Category:** Anticonvulsant, Hydantoin
- **Uses:** treatment of seizures refractory to phenobarbital. Can administer with lorazepam for rapid onset seizure control.
- **Dosage and Administration:**
  
  **Note:** Fosphenytoin is expressed as phenytoin equivalents (PE). (Fosphenytoin 1 mg PE = phenytoin 1 mg)

Dosage and Administration con’t:
Loading dose: 15 to 20 mg PE/kg IM or IV infusion over at least 10 minutes.
Maintenance dose: 4 to 8 mg PE/kg q 24 hours IM or IV slow push. Begin 24 hours after load.
Maximum rate of infusion 1.5 mg PE/kg per minute.
Flush with saline before and after administration.

Fosphenytoin (continued)

- **Adverse Reactions:** Signs of toxicity include drowsiness that is dose and rate dependent. Minor irritation at IV site.

- **Mechanism of Action:** Fosphenytoin is water-soluble and is a prodrug of phenytoin. It is rapidly converted by phosphatases in the blood and tissue. Has no known pharmacologic activity before conversion to phenytoin.

Fosphenytoin (continued)

○ **Mechanism of Action continued:**
  Phenytoin works by stabilizing neuronal membranes and decreasing seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex.

○ **Pharmacokinetics:**
  Pharmacokinetics for fosphenytoin-derived phenytoin are the same as those for phenytoin.

Maintenance Care

- Pain medication and sedation were provided for this infant during the cooling process. A fentanyl or morphine drip would be appropriate for the treatment of pain during this cooling process and midazolam for sedation.

- The infant is also paralyzed with pancuronium in an effort to decrease shivering that might increase the body temperature during the cooling process.
Fentanyl

- **Pharmacologic Category:** Analgesic, Narcotic; General Anesthetic

- **Usage:** Sedation, relief of pain; adjunct to general or regional anesthesia

- **Dosing:**
  - **Sedation and Analgesia:** 0.5 to 4 mcg/kg per dose, repeated required q 2-4 hrs.
  - **Route:** slow IV push
  - **Infusion Rate:** 1 to 5 mcg/kg per hour. May rapidly develop tolerance with constant infusion.

- **Anesthesia:** 5 to 50 mcg/kg/per dose.


Fentanyl (continued)

- **Adverse Reactions:**

  Cardiovascular: Bradycardia, cardiac arrhythmia, hypertension, hypotension, tachycardia

  Renal: Urinary retention may occur with continuous infusions.

  Respiratory: Apnea, hypoxia, respiratory depression.


Fentanyl (continued)

- **Mechanism of Action:** Interacts with opiate receptors decreasing pain impulse transmission at the spinal cord level and higher in the CNS, thus increasing the pain threshold, altering pain reception and inhibiting ascending pain pathways.

- **Pharmacodynamics:** May have respiratory depression lasting longer than the analgesic effect
  
  Onset of action:
  
  - I.M.: 7-15 minutes
  
  - I.V.: almost immediate

  Duration:
  
  - I.M.: 1-2 hours
  
  - I.V.: 30-60 minutes

- **Pharmacokinetics**

  Newborn Clearance: may be correlated to gestational age and birth weight.


Morphine

- **Therapeutic Category:** Analgesic; narcotic

- **Uses:** Sedation. Treatment of opioid dependence and neonatal abstinence syndrome.

- **Dosage and Administration:** 0.05 to 0.2 mg/kg per dose IV over at least 5 minutes, IM, or SC. May be repeated as needed, usually q 4 hours. Continuous infusion: give loading dose of 100 to 150 mcg/kg over one hour followed by 10-20 mcg/kg per hour.

Morphine (continued)

- **Dosage and administration con’t:**
  Treatment of opioid dependence: begin at most recent IV morphine dose equivalent. Taper 10 to 20% per day as tolerated. Oral dose is 3-5 times IV dose.
  Initial treatment of neonatal abstinence syndrome: 0.03-0.1 mg/kg per dose po q 3-4 hours, wean by 10-20% every 2 to 3 days based on scoring. Use a 0.4 mg/ml dilution.

- **Adverse Reactions:** Marked respiratory depression, hypotension, bradycardia, and transient hypotonia. An ileus and delayed gastric emptying and urine retention may occur. Tolerance may develop after prolonged use, wean slowly.

Morphine (continued)

- **Mechanism of action:** binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering patient perception of and response to pain. Also causes generalized CNS depression.

- **Pharmacodynamics:**
  Oral solution: Peak: 1 hr. Duration: 2-5 hours.
  IM injection: Peak: 30-60 min. Duration: 3-5 hours.
  IV injection: Peak: 20 min. Duration: 3-5 hours.

Morphine (continued)

- **Pharmacokinetics:**
  Distribution: to skeletal muscle, liver, kidneys, lungs, intestinal tract, spleen, brain, and into breast milk, crosses placenta.
  Protein binding: premature infants < 20%.
  Metabolism: in the liver via glucuronide conjugation
  Half-life:
  Premature Infants: 10-20 hours
  Neonates: 7.6 hours, range 4.5 -13.3 hrs.
  Clearance:
  Premature: 0.5-3 ml/minute/kg
  Neonates 1-7 days: median 5.5 mL/min/kg, range 3.2-8.4 ml/min/kg
  Neonates 8-30 days: median 7.4 ml/min/kg, range 3.4-13.8 ml/min/kg

Midazolam

**Therapeutic Category:** Sedative/Hypnotic, anticonvulsant

**Usage:** Conscious sedation, treatment of refractory seizures, anxiolysis, and amnesia prior to a procedure or before anesthesia

**Administration:**

**Sedation:**
- **IV:** 0.5 to 0.15 mg/kg over at least 5 minutes. Repeat as needed q2-4hrs.
- **Continuous IV infusion:** 0.01 to 0.06 mg/kg per hour (10 to 60 mcg/kg/hour). May need to be increased with development of tolerance and/or increased clearance.
- **Intranasal:** 0.2 to 0.3 mg/kg per dose using 5-mg/ml injectable form.
- **Sublingual:** 0.2 mg/kg per dose using 5-mg/ml injectable form mixed with a small amount of flavored syrup.
- **Oral:** 0.25 mg/kg per dose using Versed® oral syrup.


Midazolam (continued)

- **Dosage and Administration Continued:**
  Anticonvulsant: Loading dose: 0.15 mg/kg (150 mcg/kg) IV over at least 5 minutes, followed by Maintenance Infusion: 0.06 to 0.4 mg/kg per hour (1 to 7 mcg/kg per minute).

- **Adverse Reactions/ Precautions:**
  **Black Box Warning:** Midazolam has been associated with respiratory depression and arrest when used for sedation in a non-critical care setting. Rapid administration of midazolam has been associated with severe hypotension and seizures in neonates. Nasal administration may cause a burning sensation.

Midazolam (continued)

- **Mechanism of Action:** “Depresses all levels of CNS, including the limbic and reticular formation, by binding to the benzodiazepine site on the gamma-aminobutyric acid (GABA) receptor complex and modulating GABA, which is a major inhibitory neurotransmitter in the brain.”

- **Pharmacodynamics: Onset of Action**
  Children:
  I.M.: within 5 minutes
  I.V.: within 5 minutes
  Intranasal: within 5 minutes
  Duration:
  I.M.: Mean: 2 hours, up to 6 hours
  I.V.: 20-30 minutes
  Intranasal: 30-60 minutes
  Note: Full recovery may take more than 24 hours

Midazolam (continued)

- **Pharmacokinetics:**
  
  Distribution: $V_d$:
  
  Preterm infants (n=24; GA: 26-34 weeks; PNA: 3-11 days)
  
  Median 1.1L/kg (range: 0.4-4.2 L/kg)

  Half-life, elimination: Increased with acute renal failure.

  Preterm Infants (n=24; GA: 26-34 weeks; PNA: 3-11 days)

  Median: 6.3 hours (range: 2.6-17.7 hours)

  Neonates: 4-12 hours; seriously ill neonates: 6.5-12 hours

Midazolam (continued)

- **Pharmacokinetics Continued**
  - Elimination: 63-80% excreted as alpha-hydroxy-midazolam glucuronide in urine; 2-10% in feces, < 1% eliminated as unchanged drug in the urine.
  - Clearance:
    - Preterm (n=24; GA: 26-34 weeks; PNA 3-11 days):
      - Median: 1.8 mL/minute/kg
      - (range: 0.7-6.7 mL/minute/kg)
    - Neonates < 39 weeks GA: 1.17 mL/minute/kg
    - Neonates > 39 weeks GA: 1.84 mL/minute/kg

- **Nursing Implications:** Abrupt discontinuation after prolonged use may result in withdrawal symptoms.

Pancuronium

- **Therapeutic Category:** Neuromuscular Blocker Agent, Nondepolarizing: Skeletal Muscle Relaxant, Paralytic

- **Uses:** Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation

- **Mechanism of Action:** Nondepolarizing neuromuscular blocker which blocks acetylcholine from binding to receptors on motor endplate thus inhibiting depolarization.


Pancuronium (continued)

- Pharmacodynamics:
  Maximum effect:
  IV injection: within 2-3 minutes.
  Duration:
  40-60 minutes (dose dependent)

- Pharmacokinetics:
  Protein binding: 87%
  Metabolism: 30-40% in the liver
  Elimination: Primarily in urine (60%) as unchanged drug and in bile (40%).

Pancuronium (continued)

- **Adverse Reactions/Precautions:**
  - Cardiovascular: tachycardia, hypotension, hypertension
  - Dermatologic: Rash, erythema
  - Gastrointestinal: Excessive salivation
  - Neuromuscular & skeletal: Muscle weakness
  - Respiratory: wheezes and brochospasm

**Black Box Warning:** Should be administered by trained individuals familiar with actions, characteristics, and hazards.


What is HIE?

- Hypoxic-Ischemic Encephalopathy
- Acute brain injury due to prenatal, intrapartum, or postnatal hypoxic events
- Hypoxia and ischemia leading to neurologic dysfunction
- It is also known as perinatal asphyxia or neonatal encephalopathy
- Occurs most often in term or near-term infants.
Incidence of HIE

- 1-2/1000 live term births (developed countries)
- 10-20% mortality (postnatal)
- 25% childhood disabilities
  - Cerebral palsy
  - Epilepsy
  - Mental retardation
  - Learning disabilities

Clinical Presentation of HIE

- Lethargy to stupor/coma
- Decreased/ no spontaneous activity
- Flexion /decerebrate posture
- Hypotonia
- Seizures
- Weak or absent reflexes
- Abnormal pupil reactions
- Arrhythmias
- Periodic breathing/apnea
High Risk Factors for HIE

Fall into one of three categories:

- **Preconceptual Factors**
  - Previous prenatal death
  - Multiparity
  - Insulin dependent diabetes
  - Thyroxine exposure
  - Thyroid disease
High Risk Factors for HIE

- **Antepartum factors**
  - Preeclampsia
  - Fetal growth retardation
  - Multiple birth
  - Placenta previa/placental abruption
  - Antepartum hemorrhage
  - Threatened miscarriage
  - Prolonged rupture of membranes
  - Polyhydramnios
High Risk Factors for HIE

○ **Intrapartum Factors**
  - Induced delivery
  - Operative delivery
  - Instrumental delivery
  - Oxytocin augmentation
  - Breech presentation
  - Prolonged second stage
  - Cord prolapse
HIE consists of two Insults: Primary and Secondary

Primary Insult- can occur prenatal, intrapartum or postnatal and is characterized by:

- Reduced arterial oxygen content (hypoxia)
- Reduced cerebral blood flow (ischemia)
- ATP Failure- ATP is the primary energy source of the cell
- Gas exchange impaired with hypoxia, hypercarbia and acidosis (asphyxia)
- Tissue acidosis prominent
- Injury reversible to some degree
HIE consists of two Insults: Primary and Secondary

Secondary Insult

- Occurs 6-12 hours after birth
- Tissue injury occurs when blood flow returns and molecular oxygen is reintroduced to the tissues
- During post-ischemic reperfusion cytotoxic oxygen-derived free radicals are generated
- The highest post-asphyxial cerebral blood flow is correlated with the severity of brain damage.
Staging of Neonatal Encephalopathy per Sarnat & Sarnat
Stage 1 (Mild encephalopathy)

- Hyperalert
- Normal tone/reflexes
- Myoclonus
- Hyperresponsiveness to stimulation
- Tachycardia
- Reactive, dilated pupils
- Normal EEG
Stage 2 (Moderate Encephalopathy)

- Lethargy
- Hypotonia
- Increased tendon reflexes
- Myoclonus
- Frequent seizure activity
- Weak suck
- Incomplete Moro reflex
- Overactive dolls-eye reflex
- Pupils constrictive, reactive
- Periodic respirations may be present
Stage 3 (Severe Encephalopathy)

- Deterioration in level of consciousness
- Mechanical ventilation required
- Apnea/bradycardia
- Seizures within first 12 hours of life
- Severe hypotonia/flaccidity
- Absent reflexes
- Doll’s eye reflex weak or absent
- Pupils often unequal; variable reactivity/poor light reflex
- Deterioration occurs within 24-72 hours
- Death
Diagnosis of HIE

- Look for events which could compromise blood or oxygen supply to the fetus
- No clear diagnostic test for encephalopathy due to hypoxia-ischemia
- Maternal temperature elevations increased risk
- Consider placental pathology
- Detailed neonatal neurological exam to determine degree of encephalopathy
- Most infants with encephalopathy do not have an obvious cause
Diagnostic Tools

- Cranial ultrasound
- CT
- MRI
- EEG
Therapeutic Window for Treatment

- Interval between the primary and secondary energy failure
- Initiation of therapies in animals during this latent phase were successful in reducing brain damage
- Duration of the therapeutic window ~ 6 hours in near term fetal sheep treated with brain cooling after brain ischemia.
Management of HIE

- Prompt resuscitation
- Maintain physiologic oxygenation & acid-base balance
- Homeostasis of fluid and electrolyte abnormalities
- Monitor blood volume
- Maintain perfusion
- Control seizures
- Thorough neurological exams
- Monitor and manage disturbances with other body systems
- Consider cerebral hypothermia
Management Specifics

- **Ventilation**
  - Maintain the CO$_2$ within normal range (35-45)
  - High CO$_2$ increases cerebral blood flow
  - Low CO$_2$ decreases cerebral blood flow

- **Perfusion**
  - Promptly treat hypotension
  - Avoid hypertension

- **Fluid Status**
  - Establish immediate access (UVC or PIV) and start IVF
  - Watch urine closely for ATN or SIADH in the first 48 hours – dec. total fluids to 60 ml/kg/day if present
More Management Specifics

- **Blood Glucose**
  - Establish immediate access (UVC or PIV)
  - Maintain in normal range
  - Avoid hypoglycemia

- **Seizure**
  - Treat clinical seizures

- **Monitor Electrolytes**

- **Coagulation** (disseminated intravascular coagulation [DIC] may occur)
  - Monitor platelets, PT/PTT
Why Hypothermia?

- Cooling brain temperature 3-5 degrees reduces brain injury in animals and adults
- Prevents edema
- Temperature reduction decreases the metabolic rate of the brain by 5.3% and reduces the amount of oxygen required by the brain by 6-7%.
- May reduce the severity of the reperfusion injury to the brain, protect neurons by lowering cerebral metabolism, and delaying the reperfusion injury allowing time for other interventions.
- Inhibits platelet-activating factor, inflammatory cascade.
Reduces the Extent of Brain Injury

- Reduction of infarct size
- Decrease in neuronal cell loss
- Retention of sensory motor function
- Preservation of hippocampal structures
- Recovery of electroencephalographic activity
Who Benefits?

- Outcomes of infants who were cooled showed decreased rates of cerebral palsy and mental impairments.
- Infants with moderate HIE improved the most. The effects of cooling were not improved for infants with either mild or severe HIE.
Exclusion Criteria

Strong Clinical indicators of:

- Severe Sepsis
- Meningitis
- Pneumonia
- Active Bleeding
Different Cooling Techniques

- Selective head Cooling: thought to decrease the systemic effects of hypothermia but may not be as effective in cooling the deep regions of the brain. Head cooling penetrates 1 cm.

Different Cooling Techniques

- Whole Body Cooling: Cooling all areas of the brain could only be achieved by lowering the core temperature of the baby.
- While both head and body cooling are associated with reduction in brain injury following HIE, whole body cooling results in more consistency in temperature regulation.
- Temperature regulation is beneficial because small fluctuations in temp may result in varied neurological protection.
Different Cooling Techniques

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Whole Body Cooling
Cooling Techniques
Complications of Whole-Body Cooling

- Temperature instability
- Thrombocytopenia
- Disseminated intravascular coagulation or DIC
- Hypoxemia
- Mild meningeal or subdural bleeding
- Subcutaneous fat necrosis


How Mild to Moderate Hypothermia Affects Drug Metabolism

- The medications used in this presentation have been listed with the normal pharmacodynamics and pharmacokinetics up to this point, however, hypothermia may affect the half-life, distribution and elimination. This section of the presentation covers changes that may occur.
How Mild to Moderate Hypothermia Affects Drug Metabolism

Affects both:
- pharmacokinetics or distribution and clearance
- pharmacodynamics or drug effects

Changes are due to altered enzyme kinetics and/or altered blood flow affecting tissue distribution and hepatic and renal clearance

Effect of Hypothermia on medication

- **Morphine** during hypothermia:  
  - decreases metabolism  
  - increases plasma concentration  
  - Risk of toxic levels at standard doses  
  - This is at a temperature of 33-34° C

Recommendations:  
- Titrate dose to effect  
- Consider a lower starting dose

Sedation and Pain Control Drugs

Effect of Hypothermia on medication

- **Fentanyl** during hypothermia:
  - decreases metabolism and clearance
  - increases plasma concentration
  - decreases volume of distribution
  - may be sequestered in periphery
  - this is at a temperature of < 34°C

Recommendations:
- titrate dose to effect
- consider a lower starting dose

- Fentanyl during rewarming:
  - monitor for overdosing if the fentanyl was started before cooling

Sedation and Pain Control Drugs

Effect of Hypothermia on Medication

- **Midazolam** during hypothermia:
  - decrease in metabolism and clearance
  - increase in volume of distribution
  - 5-fold increase in plasma concentration
  - this is at a temperature < 35°C

Recommendations:
- Titrate dose to effect
- Consider a lower starting dose

- Midazolam during rewarming:
  - Sharp decrease during rewarming
  - Monitor for withdrawal during rewarming

Anticonvulsant

Effect of Hypothermia on Medication

- Phenobarbital during hypothermia:
  - decrease in urinary excretion of metabolites
  - increase in urinary excretion of unchanged drug
  - increase in plasma concentration
  - this is at a temperature of 31-32°C

Recommendations:
- Monitor levels at initiation, hypothermia and rewarming periods
- Risk of overdosing during cooling

Anticonvulsant

Effect of Hypothermia on Medication

- **Phenytoin** during hypothermia:
  - decrease in metabolism and clearance
  - increase in plasma concentration
  - risk of overdosing during cooling
  - this is at a temperature of 34°C

Recommendations:
- Monitor levels at initiation, during hypothermia and during rewarming periods

Phenytoin during rewarming:
- risk of underdosing after rewarming

Antibiotic

Effect of Hypothermia on Medication

- **Gentamicin** during hypothermia:
  - decreased clearance, volume of distribution
  - increased half-life
  - this is at a temperature of 29°C
  - no change in metabolism at 35°C

Recommendations:
- Monitor levels at initiation, and during hypothermia and rewarming period

Gentamicin during rewarming:
- risk of underdosing after rewarming

Continued Patient Care and Discharge

- After 72 hours of cooling the infant is gradually rewarmed (an increase of 0.2°C every 30 minutes).
- The ventilator was gradually weaned and the infant was extubated.
- No further seizure activity was noted.
- A neurological consult was obtained to determine the need for further Phenobarbital and to determine follow-up.
- Enteral feeds progressed slowly.
- Feeding volume advanced nicely, but the infant was a poor po feeder.
Discharge and Follow-Up

- The infant was discharged home with his mother.
- Feedings were set with a minimum amount to be fed per feeding.
- Early Intervention was arranged by the physical therapist.
- Follow-up with the NICU Neurodevelopmental Clinic was scheduled for 3 months.
References


References
