Pediatric Parenteral Nutrition

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The University of Illinois College of Pharmacy

The speaker has no conflict to disclose.

Pediatric Parenteral Nutrition
Goals and Objectives

• At the end of this lecture, participants will be able to…
• Describe the nutritional needs specific to different age groups in the pediatric population
• List the requirements for macronutrients and electrolytes specific to different age groups in the pediatric population
• Accurately formulate a pediatric parenteral nutrition order

Indications for Parenteral Nutrition

• Patient is unable to meet nutritional needs by the enteral route in 5 days
• Intensive care low birth weight infants
• Severe malnutrition
• Clinical conditions such as intractable vomiting or diarrhea
• Hypercatabolic ICU patients
• Patients with short bowel syndrome that cannot meet their needs enterally
Nutritional Goals

Parenteral Nutrition Access

Central Line
- Administer higher osmolality
- Risk of infection
- Mechanical issues

Peripheral Line
- Not to exceed 800 mOsm/L
- Max dextrose 10 – 12%
- Max protein 2.5%
- Calcium 10 mg/dL
- Potassium 40 mg/dL

Fluid Requirements

For kg >20
- 20 cc/kg

For kg 11 – 20
- 50 cc/kg

For kg 1-10
- 100 cc/kg
Ex. Calculate a 15 kg patient’s maintenance fluid requirements

<table>
<thead>
<tr>
<th>Patient’s Weight</th>
<th>Appropriate Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg</td>
<td>250 cc</td>
</tr>
<tr>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10 kg</td>
<td>1000 cc</td>
</tr>
</tbody>
</table>

Total: 1250 cc

**Parenteral Nutrition Order**

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>1250 gm</th>
<th>15 kg</th>
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<tbody>
<tr>
<td>Line</td>
<td>Central line</td>
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</tr>
<tr>
<td>Volume</td>
<td>125 ml (5.2 ml/hr)</td>
<td>1250 ml (52 ml/hr)</td>
</tr>
<tr>
<td>Dextrose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>- Na</td>
<td></td>
</tr>
<tr>
<td>- K</td>
<td>- Cl/Acetate</td>
<td></td>
</tr>
<tr>
<td>- Phos</td>
<td>- Ca</td>
<td></td>
</tr>
<tr>
<td>- Mg</td>
<td>MVI/Trace</td>
<td></td>
</tr>
<tr>
<td>Intralipid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Estimated Caloric Requirements**

- **Preterm Neonate**: 100 – 120 kcal/kg/day
- **Term Infant to 1 year**: 90 – 120 kcal/kg/day
- **1 – 7 years**: 75 – 90 kcal/kg/day
- **7 – 12 years**: 60 – 75 kcal/kg/day
- **12 – 18 years**: 30 – 60 kcal/kg/day
Glucose Intolerance

- Common
- Start low and titrate
- Recommended glucose infusion rate (GIR)
  - VLBW to start at 4 – 6 mg/kg/min
  - Larger neonates may tolerate 6 – 8 mg/kg/min
- Titrate by 1 – 2.5 mg/kg/min per day
- Max 10 – 14 mg/kg/min

Older Infants, Children, and Adolescents

- Begin Dextrose 10 – 12.5% and titrate

Glucose Infusion Rate

- Calculation of Dextrose %
  \( \frac{6 \times (\text{desired GIR}) \times \text{wt in kg}}{\text{rate in ml/hr} \times 100} = \% \text{ Dextrose} \)
  
  \( \frac{6 \times (6) \times 1.25 \text{ kg}}{5.2 \text{ ml/hr}} = 8.6\% \)

- Calculate GIR from % Dextrose
  \( \frac{1440 \text{ min} \times \% \text{ dextrose} \times \text{volume of tpm} \times 1000}{\text{wt in kg} \times \text{mg/kg/min}} \)
  
  \( \frac{0.086 \times 125 \text{ ml} \times 1000}{1440 \text{ min} \times 1.25 \text{ kg}} = 6 \text{ mg/kg/min} \)
Parenteral Nutrition Order

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<thead>
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<td>Dextrose</td>
<td>8.5%</td>
<td>10% - 12%</td>
</tr>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Na</td>
<td></td>
<td></td>
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<tr>
<td>- K</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>- Phos</td>
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<tr>
<td>- Ca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVI/Trace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Protein Requirements by Age and Illness Severity (g/kg/day)

<table>
<thead>
<tr>
<th>Very Low Birth weight</th>
<th>Preterm</th>
<th>Neonate</th>
<th>Infant</th>
<th>Preschool/ School age</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>2.5-3</td>
<td>2.5</td>
<td>2-2.5</td>
<td>1.5-2</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Amino acid composition

- Enzyme immaturity contributes to conditionally essential amino acids
- Formulations specific for neonates and infants
  - Trophamine, Aminosyn PF and Premasol
- Contain higher amounts of aspartate, glutamate, taurine and tyrosine
- Cysteine is added as a separate product
  - Usual dose is 40 mg/gm amino acid
**Intralipid**

- **Preterm:** Initiate at 0.5 gm/kg/day
- **Infants and children:** Initiate at 1 – 1.5 gm/kg/day
- 20% lipid emulsion preferred over 10% in infants
  - 10% has a higher phospholipid to triglyceride ratio
  - FYI 20% intralipid is 2 kcal/ml
- **Carnitine:** 2 – 10 mg/kg/day

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</tr>
<tr>
<td>Dextrose</td>
<td>8.5%</td>
<td>10% - 12%</td>
</tr>
<tr>
<td>Protein</td>
<td>2.5% (3.1 gm x 2.5 gm/kg/day)</td>
<td>1.8% (22.5 gm x 1.5 gm/kg/day)</td>
</tr>
<tr>
<td>Aminosyn</td>
<td>Trophamine</td>
<td></td>
</tr>
<tr>
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<tr>
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<td>- Mg</td>
</tr>
<tr>
<td>MVI/Trace</td>
<td>Intralipid</td>
<td>3.6 ml (0.6 gm/kg/day)</td>
</tr>
</tbody>
</table>

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**Electrolyte requirements (meq/kg/day)**

- **Preterm infants**
  - Sodium (2 – 8)
  - Potassium (1 – 5)
  - Chloride (1 – 5)
  - Magnesium (0.25 – 0.6)
  - Calcium (2 – 3.5)
  - Phosphate (1.3 – 2)

- **Term Infants and Children**
  - Sodium (2 – 5)
  - Potassium (2 – 3)
  - Chloride (2 – 3)
  - Magnesium (0.25 – 0.3)
  - Calcium (1-2)
  - Phosphate (0.5 – 1)
**Multivitamins and Trace Elements**

- Use pediatric specific products in children < 11 years old
- MVI pediatric
  - 2 ml/kg/day to a max of 5 ml
- Trace elements
  - Pediatric trace elements at 0.2 ml/kg
  - Additional selenium (Max 60 mcg)
  - Doses must be modified for renal failure and cholestasis

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</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Na</td>
<td>2 meq/kg</td>
<td>96 meq (77 meq/l)</td>
</tr>
<tr>
<td>- K</td>
<td>none</td>
<td>30 meq</td>
</tr>
<tr>
<td>- Cl/Acetate</td>
<td>All acetate</td>
<td>1 meq/kg acetate the rest CI</td>
</tr>
<tr>
<td>Phos</td>
<td>1 – 1.3 mmol/kg</td>
<td>15 mmol</td>
</tr>
<tr>
<td>- Ca</td>
<td>2.5 meq/kg</td>
<td>9.2 meq (2 gm)</td>
</tr>
<tr>
<td>- Mg</td>
<td>Based on labs</td>
<td>3 meq</td>
</tr>
<tr>
<td>MVI/Trace</td>
<td>Standard + x-tra zinc</td>
<td>Standard</td>
</tr>
<tr>
<td>Intralipid</td>
<td>3.6 ml (0.6 gm/kg/day)</td>
<td>96 ml (1.3 gm/kg/day)</td>
</tr>
<tr>
<td>Calories</td>
<td>43.3 non protein kcal</td>
<td>617 non protein kcal</td>
</tr>
<tr>
<td>Calories/kg/day</td>
<td>35 kcal/kg/day</td>
<td>41 kcal/kg/day</td>
</tr>
</tbody>
</table>
References

Pediatric Parenteral Nutrition
09-047
Kelly Kopec

Assessment

As illustrated in the patient case discussed in the lecture, what are the protein requirements in gm/kg and calorie requirements in kcal/kg for a pre-mature neonate?

a. 100 - 120 kcal/kg/day and 2.5 - 3 gm/kg protein a day
b. 70 - 120 kcal/kg and 1 – 1.5 gm/kg protein a day
c. 100 - 120 kcal/kg and 3 - 4 gm/kg protein a day
d. 40 - 75 kcal/kg and 2.5 - 3 gm/kg protein a day

What is the overall trend of nutrient requirements across age groups?

a. Calorie requirements per kg and protein requirements per kg decrease from young to old
b. Calorie requirements per kg and protein requirements per kg increase from young to old
c. Calorie requirements per kg decrease and protein requirements per kg increase from young to old
d. Calorie and protein requirements remain stable across age groups
Objectives

- Define the mechanism of action and adverse effects of opiates, benzodiazepines, alpha-antagonists and anesthetic agents
- Identify symptoms of pain and agitation in pediatric patients
- Describe symptoms of withdrawal in children and recommend a pharmacologic weaning plan to prevent withdrawal in children

What’s in your Toolbox?
**Opiates**

Bind to opiate receptors in the brain, causing inhibition of ascending pain pathways altering the perception and the response to pain

**Opiates - Adverse Drug Reactions**

- Cardiac depression, respiratory depression, CNS depression, decreased GI motility (constipation), miosis, itching (esp. morphine), nausea/vomiting, chest wall rigidity (fentanyl with ↑ rate of infusion), seizures (meperidine), GI upset with oral doses, SIADH.
- Metabolized via the liver, not removed from CVVHD; fentanyl is bound to ECMO oxygenator (often need higher doses)
- Physical and psychological dependence

**Opiates**

*Naloxone – antidote (IV, E.T)*

Reversal of iatrogenic opiate use –
- Goal – partially reverse effects to increase respiratory drive but not analgesia
- Dose: 0.0.05 – 0.01 mg/kg/dose

*Total Reversal of opiate overdose (in ER)*
- Goal – "Wake" patient up, get patient to breath, determine if overdose due to opiate
- Dose: 0.1 mg/kg/dose
Opiate Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>0.1 mg/kg q3-6h</td>
</tr>
<tr>
<td></td>
<td>Neonates: 0.05 mg/kg q1-6h</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid®)</td>
<td>0.015 mg/kg q3 - 6h</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze®)</td>
<td>0.5-1 mcg/kg q2-6h Continuous infusion 0.5-1 mcg/kg/hr (may increase as tolerance develops to 10 mcg/kg/hour)</td>
</tr>
<tr>
<td>Methadone (Dolophine®)</td>
<td>0.1- 0.2 mg/kg q 6-8h</td>
</tr>
</tbody>
</table>

Opiates

Physical tolerance to opiates develops with time, especially with fentanyl. There is no absolute “maximum” dose of opiates. Some patients may require 5-10 times the “recommended” dose due to the tolerance, which develops over time.

Benzodiazepines

MOA - Increase the activity of GABA – an inhibitory neurotransmitter
Benzodiazepines

- BZDs do not bind to the GABA receptor directly, but to a BZD receptor site on the GABA-A receptor complex (GARC). When doing so, BZDs modulate the GARC, augmenting the effects of GABA that is, it increases the effectiveness of GABA for opening the ion channel by changing the GARC's shape. (Sandford, Argyropoulos, & Nutt, 2000).

Benzodiazepines

- Sedative
- Anxiolytic
- Muscle relaxant
- Anticonvulsant
- Amnestic

Benzodiazepines

Adverse effects –
- CNS and respiratory depressant
- Cardiac arrest with rapid injection
- Myoclonic jerking in premies
- Paradoxical excitement
- Preserved with and benzyl alcohol (inj) which can result in "gasping syndrome" in neonates (> 99mg/kg/day)
- Physical and psychological dependence

Reverse "overdose" with Flumazenil 0.01 mg/kg/dose. (May provoke panic attacks and seizures in these disorders). Monitor for re-sedation.
Anesthetics – Ketamine

• NMDA receptor antagonist → general anesthesia, analgesia, neurotoxicity
• Opioid kappa receptor agonist → analgesia
• Anticholinergic activity → bronchodilation, sympathomimetic effects; increased catecholamine effects

Anesthetics – Ketamine

• New data suggests that ketamine may decrease overall use of opiates by limiting the opiate tolerance via the NMDA receptors.

Anesthetics – Ketamine

Adverse effects
• Resp depression
• Hallucinations
• Increased BP, HR, cerebral blood flow (not used for patients with ↑ICP)
• Hypersalivation
• Tonic-clonic movements
• Emergence reactions
Anesthetics – Ketamine

**Uses**
- Sedation (can augment cardiac function)
- Sedation in status asthmaticus – enhances bronchodilation
- **Contraindicated** with ↑ ICP
- Treat hallucinations and emergence reactions with low-dose barbiturate or benzodiazepine

**Dose**
- 1-2 mg/kg/dose for procedural sedation
- 0.5-2 mg/kg/hour, continuous infusion

Anesthetics - Propofol

- I.V. general anesthetic
- Produces a positive modulation of the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) through GABA-A receptors
- Sedative
- Anti-epileptic
- Anxiolytic
Anesthetics - Propofol

• Fat-soluble compound, containing eggs, soybean oil and sulfites (generic brand) any of which can cause allergic reactions.
• Quick recovery from anesthesia
• Nausea & vomiting are less than other anesthetics

Anesthetics - Propofol

Procedural Sedation
Propofol sedation has been used for:
• elective oncology procedures
• dermatologic procedures
• gastrointestinal endoscopy
• imaging (MRI, CT scan)
Dose 1-2 mg/kg/dose; repeat doses or follow with continuous infusion 200 mcg/kg/minute

Anesthetics - Propofol

ICU sedation
Approved for Adult population only
1- 4.5 mg/kg/hour (15-75 mcg/kg/minute)
Used with opioid for pain management
Associated with “Propofol Infusion Syndrome (PRIS)”; use is limited to 3 days duration
Propofol Infusion Syndrome (PRIS)

- Usually associated with traumatic brain injury
- Many cases have resulted in death
- Myocardial dysrhythmias
- Metabolic acidosis
- Increased serum potassium
- Rhabdomyolysis
- Lipemia

Propofol (Diprivan)
Adverse Reactions with Prolonged Infusion - Pediatric Experience

- April 2005, FDA reports the deaths of 21 patients (<16 yr) after propofol administration for nonprocedural sedation.

Propofol

Adverse drug reactions
PRIS
- Painful infusion - may pre-treat with Lidocaine
- 1-3mg (0.1-0.3ml 10% Lidocaine) or dilute with D5W
- Hypotension
- Respiratory depression
- Zinc deficiency (Diprivan brand only)
- Green-colored urine
- Gasing syndrome (infants) due to benzyl alcohol
- Hyperlipidemia
- Allergic reaction
- Agitation, anxiety upon abrupt withdrawal of infusion
Summary- Propofol

Phenolic, fat-soluble anesthetic agent
- Sedative
- Has a role in sedation for imaging, short procedures (Sedation-trained personnel should be involved with administration)
- NOT recommended for pediatric ICU sedation
- Associated with propofol infusion syndrome
- Monitor BP, HR, RR
- Green urine, may burn if given peripherally

Alpha agonists
- Clonidine and Dexmedetomine
  Prototype agent is clonidine
  - More recent applications in clinical practice
    - Sedation
    - Behavior disorders (ADHD)
    - Drug withdrawal
    - Hypertension
  - Problem - α1 effects → hypotension
  - Solution – 2nd generation - ↑ α2 specificity

Dexmedetomine

Mechanism of Action

- The sedative and anxiolytic effects result primarily from its activity in the locus ceruleus. Stimulation of alpha2-adrenergic receptors at this site reduce central sympathetic output, resulting in increased firing of inhibitory neurons.
- Inhibition of alpha 2 receptors in the dorsal horn of the spinal cord modulates pain response
Dexmedetomidine

Adverse Drug Reactions

- CV: Hypotension, Bradycardia, Hypertension
- Pulmonary: Increased resting PaCO2, obstructive apnea, Increase MPAP, PVR?
- CNS – Ineffective analgesia, proconvulsant? Decrease CPP?
- vomiting (4%), nausea (11%)
- fever (5%)
Dexmedetomidine

Sedation during mechanical ventilation

Midazolam loading dose + 0.1mg/kg/hr
Dexmedetomidine 0.25 mcg/kg + 0.25mcg/kg/hr
Dexmedetomidine 0.5 mcg/kg/ + 0.5 mcg/kg/hr

- No differences in sedation or (BIS) scores
- The children in the high dose dexmedetomidine group required less morphine than the children given midazolam.
- Dexmedetomidine (0.25 mcg/kg/hr) = midazolam (0.22 mg/kg/hr) < (0.5 mcg/kg/hr)


Dexmedetomidine

Sedation during mechanical ventilation

Buck et al, used dexmedetomidine to assist extubation; for children w/ chronic neurologic impairment

No loading doses; continuous infusion 0.1-0.7 mcg/kg/hour along with opiates.
Treatment was continued for < 33 hours.
Hypotension was experienced in 1 patient.

Dexmedetomidine

Imaging Sedation

- CT imaging: bolus of 2 mcg/kg over 10 min followed by an infusion of 1 mcg/kg/hr resulted in success with exam. However bradycardia (18%) and hypotension (30%) occurred. (250 pts)
- MRI sedation: 2-3 mcg/kg bolus followed by infusion (1-2 mcg/kg/hr) Bradycardia resulted in 16% patients. (747 pts)
- Conclusion: anticipate these possible hemodynamic effects and avoid dexmedetomidine in those patients who may not tolerate fluctuations in HR and blood pressure.

Dexmedetomidine
Iatrogenic Opiate and Benzodiazepine Withdrawal

- Retrospective study; 7 infants: 3 to 24 months of age
- Continuous fentanyl infusion, supplemented with midazolam
- Withdrawal documented via Finnegan score ≥ 12.
- Dexmedetomidine: 0.5 mcg/kg/hr, followed with 0.5 mcg/kg/hr.
- Subsequent Finnegan scores were ≤ 7 at all times (median 4)
- Two patients required increased doses. They received higher doses of fentanyl (8.5 +/- 0.7 versus 4.6 +/- 0.5 mcg/kg/hr)
- No adverse hemodynamic or respiratory effects were noted

Tobias JD - J Opioid Manag - 01-JUL-2006; 2(4): 201-5

Summary - Dexmedetomidine

- Centrally-acting Alpha 2 agonist; inhibits norepinephrine release
- Sedative, analgesic, and hypotensive effects
- Has a role in sedation for imaging, procedures
- Limited role for ICU sedation (continuous infusion)
- Monitor BP, HR
- Do not stop prolonged infusion abruptly
- REMEMBER - mcg/kg/hour – not per minute

Sedation
Propofol compared to Ketamine, Versed and Fentanyl

<table>
<thead>
<tr>
<th>Reference</th>
<th>Procedures</th>
<th>Drug regimen</th>
<th>Apgas (%)</th>
<th>Hypo T (%)</th>
<th>Static Agitation (%)</th>
<th>Overall adverse effects requiring intervention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issues</td>
<td>BMA, TEE, LP, IT, IM, CT, CL, B, W</td>
<td>P 2.5mg/kg + 200 mcg/kg/min</td>
<td>17</td>
<td>10</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Bassett</td>
<td>BMA, TEE, LP, IT, IM, CT, CL, B, W</td>
<td>M 0.1mg/kg + K 2.0mg/kg + F 2.0mcg/kg</td>
<td>6</td>
<td>4</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Laster</td>
<td>USS, Fractures, burns</td>
<td>P 1.0mg/kg + F 3.0mg/kg</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Taylor</td>
<td>LP, BMA, E, TEE</td>
<td>M 0.05-0.1 mg/kg + K 1.0mg/kg</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>25%</td>
</tr>
<tr>
<td>Wanting</td>
<td>LP, TEE, BMA, CL, E, TEE</td>
<td>P 1.0mg/kg (max 3.0mg/kg)</td>
<td>6</td>
<td>50</td>
<td>0</td>
<td>67</td>
</tr>
</tbody>
</table>

- MAP = Mean Arterial Pressure, TEE = Transesophageal Echocardiogram, LP = Lumbar Puncture, IT = Intrathecal injection, IM = Intramuscular injection, CT = Computed Tomography, CL = Central Line Placement, B = Bronchoscopy, W = Wound Care, R = Radiation, I = Imaging, E = Endoscopy

**Dexmedetomidine or Propofol?**

- Koroglu compared dexmedetomidine and propofol in children undergoing MRI. (50 children – 2 groups)
- Dexmedetomidine (D) 1 mcg/kg + 0.5 mcg/kg/hour
- Propofol (P) 3 mg/kg + 100 mcg/kg/minute.
- Measured ability to complete the procedure
- Monitored: MAP, heart rate, O₂ saturation, and RR
- Results:
  - P and D equally effective in sedating patients
  - Onset of sedation, recovery, and discharge time were significantly shorter in group P
  - MAP, heart rate, and RR decreased in both groups but MAP and RR were significantly lower in group P than in group D during sedation. Desaturation was observed in four children of group P.
RESTORE Study
Multi-center pediatric Pain and Sedation Study, primary investigator – Martha Curley
We will utilize two new scales to measure pain and withdrawal in pediatric ICU patients.
SBS – pain and sedation measure
WAT-1 – withdrawal measure

State Behavioral Scale (SBS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>Unresponsive</td>
<td>No attention to usual stimuli or provider, no response to noxious stimuli, no active or passive movements, no attempt to contact provider</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Partial attention to usual stimuli or provider, no response to noxious stimuli, limited active or passive movements, no attempt to contact provider</td>
</tr>
<tr>
<td>0</td>
<td>Alert</td>
<td>Partial attention to usual stimuli, partial to no response to noxious stimuli, voluntary movements, attempts to contact provider</td>
</tr>
<tr>
<td>1</td>
<td>Active</td>
<td>Full attention to usual stimuli, response to noxious stimuli, active voluntary movements, attempts to contact provider</td>
</tr>
<tr>
<td>2</td>
<td>Agitated</td>
<td>Increased Attention, increased AP and vital signs, increased muscle tone,呻吟, agitation, increased sedation score,References to agitated behavior in children.</td>
</tr>
</tbody>
</table>
Withdrawal Assessment Tool (WAT-1)

<table>
<thead>
<tr>
<th>Patient Identifier</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Deidentified)</td>
<td>(Time)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any crying without reason</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Any sadness or crying</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Temperature (°C/F)</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Any gross motor abnormality</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Note</th>
<th>(WAT-1)</th>
<th>(Interobserver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Task</th>
<th>Task Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor Briskness</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor Tone</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprioceptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tone in soft sounds (dB)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score (0-12)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

“*You can’t just switch them. If your wife asked you to change the baby, she probably meant the diaper.*”
<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
</table>
| -3    | Unresponsive                             | No spontaneous respiratory effort  
No cough or coughs only with suctioning  
No response to noxious stimuli  
Unable to pay attention to care provider  
Does not distress with any procedure (including noxious)  
Does not move |
| -2    | Responsive to noxious stimuli             | Spontaneous yet supported breathing  
Coughs with suctioning/repositioning  
Responds to noxious stimuli  
Unable to pay attention to care provider  
Will distress with a noxious procedure  
Does not move/occasional movement of extremities or shifting of position |
| -1    | Responsive to gentle touch or voice       | Spontaneous but ineffective non-supported breaths  
Coughs with suctioning/repositioning  
Responds to touch/voice  
Able to pay attention but drifts off after stimulation  
Distresses with procedures  
Able to calm with comforting touch or voice when stimulus removed  
Occasional movement of extremities or shifting of position |
| 0     | Awake and Able to calm                   | Spontaneous and effective breathing  
Coughs when repositioned/Occasional spontaneous cough  
Responds to voice/No external stimulus is required to elicit response  
Spontaneously pays attention to care provider  
Distresses with procedures  
Able to calm with comforting touch or voice when stimulus removed  
Occasional movement of extremities or shifting of position/increased movement (restless, squirming) |
| +1    | Restless and difficult to calm           | Spontaneous effective breathing/Having difficulty breathing with ventilator  
Occasional spontaneous cough  
Responds to voice/ No external stimulus is required to elicit response  
Drifts off/ Spontaneously pays attention to care provider  
Intermittently unsafe  
Does not consistently calm despite 5 minute attempt/unable to console  
Increased movement (restless, squirming) |
| +2    | Agitated                                 | May have difficulty breathing with ventilator  
Coughing spontaneously  
No external stimulus required to elicit response  
Spontaneously pays attention to care provider  
Unsafe (biting ETT, pulling at lines, cannot be left alone)  
Unable to console  
Increased movement (restless, squirming or thrashing side-to-side, kicking legs) |
**WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)**

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<table>
<thead>
<tr>
<th>Patient Identifier</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time:</td>
</tr>
</tbody>
</table>

**Information from patient record, previous 12 hours**

<table>
<thead>
<tr>
<th>Any loose/watery stools</th>
<th>No = 0</th>
<th>Yes = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any vomiting/wretching/gagging</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Temperature &gt; 37.8°C</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
</tbody>
</table>

**2 minute pre-stimulus observation**

<table>
<thead>
<tr>
<th>State</th>
<th>SBS¹ ≤ 0 or asleep/awake/calm = 0</th>
<th>SBS¹ &gt; +1 or awake/distressed = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>None/mild = 0</td>
<td>Moderate/severe = 1</td>
</tr>
<tr>
<td>Any sweating</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Uncoordinated/repetitive movements</td>
<td>None/mild = 0</td>
<td>Moderate/severe = 1</td>
</tr>
<tr>
<td>Yawning or sneezing</td>
<td>None or 1 = 0</td>
<td>&gt;2 = 1</td>
</tr>
</tbody>
</table>

**1 minute stimulus observation**

| Startle to touch | None/mild = 0 | Moderate/severe = 1 |
| Muscle tone | Normal = 0 | Increased = 1 |

**Post-stimulus recovery**

| Time to gain calm state (SBS¹ ≤ 0) | < 2min = 0 | 2 - 5min = 1 | > 5 min = 2 |

**Total Score (0-12)**

**WITHDRAWAL ASSESSMENT TOOL (WAT – 1) INSTRUCTIONS**

- Start WAT-1 scoring from the first day of weaning in patients who have received opioids+/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days). Continue twice daily scoring until 72 hours after the last dose.
- The Withdrawal Assessment Tool (WAT-1) should be completed along with the SBS¹ at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS¹ assessment provides a standard stimulus for observing signs of withdrawal.

**Obtain information from patient record (this can be done before or after the stimulus):**

- **Loose/watery stools**: Score 1 if any loose or watery stools were documented in the past 12 hours; score 0 if none were noted.
- **Vomiting/wretching/gagging**: Score 1 if any vomiting or spontaneous wretching or gagging were documented in the past 12 hours; score 0 if none were noted.
- **Temperature > 37.8°C**: Score 1 if the modal (most frequently occurring) temperature documented was greater than 37.8°C in the past 12 hours; score 0 if this was not the case.

- **State**: Score 1 if awake and distress (SBS¹: ≥ +1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative (SBS¹ ≤ 0).
- **Tremor**: Score 1 if moderate to severe tremor observed during the 2 minutes prior to the stimulus; score 0 if no tremor (or only minor, intermittent tremor).
- **Sweating**: Score 1 if any sweating during the 2 minutes prior to the stimulus; score 0 if no sweating noted.
- **Uncoordinated/repetitive movements**: Score 1 if moderate to severe uncoordinated or repetitive movements such as head turning, leg or arm flailing or torso arching observed during the 2 minutes prior to the stimulus; score 0 if no (or only mild) uncoordinated or repetitive movements.
- **Yawning or sneezing > 1**: Score 1 if more than 1 yawn or sneeze observed during the 2 minutes prior to the stimulus; score 0 if 0 to 1 yawn or sneeze.

**1 minute post-stimulus observation:**

- **Startle to touch**: Score 1 if moderate to severe startle occurs when touched during the stimulus; score 0 if none (or mild).
- **Muscle tone**: Score 1 if tone increased during the stimulus; score 0 if normal.

**Post-stimulus recovery:**

- **Time to gain calm state (SBS¹ ≤ 0)**: Score 2 if it takes greater than 5 minutes following stimulus; score 1 if achieved within 2 to 5 minutes; score 0 if achieved in less than 2 minutes.

**Sum the 11 numbers in the column for the total WAT-1 score (0-12).**

Post-test questions

1) Dexmedetomidine (choose one):
   a) Usually causes hypertension and shivering
   b) Blocks the alpha2-adrenergic receptors and increases central sympathetic output
   c) May be used for sedation for imaging procedures or short-term ICU sedation
   d) Can used freely with patients with cardiac disorders

2) Adverse effects of the benzodiazepines may include:
   a) CNS and respiratory depression
   b) Cardiac arrest with rapid injection
   c) Myoclonic jerking in premature infants
   d) Paradoxical excitement
   e) Preserved with and benzyl alcohol (inj) which can result in “gasing syndrome” in neonates (> 99mg/kg/day)
   f) Physical and psychological dependence

   A. a, b, and d
   B. a,b,c,d, and e
   C. All of the above

3) True or False:

   An SBS score of +1 indicates that the patient is well-sedated and requires no further intervention
Medication Dosing in Pregnancy

Catherine Stika, MD
Assoc Professor in Obstetrics & Gynecology
Northwestern University
September 12, 2009

Overview

- Conflict of Interest Statement: I or my spouse/partner have no actual or potential conflict of interest in relation to this activity.
- Pregnancy is an FDA “Special Population”
- Discuss the physiologic changes in pregnancy that impact drug dosing in the obstetrical patient by examining 3 drugs
  - Low molecular weight heparins
  - Lamotrigine
  - Digoxin

Low Molecular Weight Heparins

- Who in the audience is a hospital-based vs community-based pharmacist?
  - A. hospital-based
  - B. community based
Low Molecular Weight Heparins

- Of those of you who are hospital-based, how many of you have dosing guidelines for LMWHs?
  - A. Yes
  - B. No

- Of those with LMWH dosing guidelines, how many of you have specific (different) guidelines for use in pregnancy?
  - A. Yes
  - B. No

Low Molecular Weight Heparins

- The Vd of LMWHs is approximately equivalent to which space?
  - A. Total body water, or
  - B. Plasma volume

- LMWHs are primarily cleared via which route?
  - A. Hepatic
  - B. Renal

LMWHs in Pregnancy

- What happens to LMWH Vd in pregnancy?
  - A. Goes up
  - B. Goes down
  - C. Stays the same
Plasma Volume Expansion

- Begins at 6 - 8 weeks’ gestation
- Peaks at ~ 32 weeks’ gestation
- Increases 1200 - 1600 mL above the nonpregnant state, or ~ 40% greater
- Increase in plasma volume is related to fetal number: PV increase in triplets is almost double that in singletons

LMWHs in Pregnancy

- What happens to LMWH renal clearance in pregnancy?
  - A. Goes up
  - B. Goes down
  - C. Stays the same

GFR during Pregnancy and Postpartum

Why does GFR go up?

- GFR is proportionate to cardiac output
- Cardiac output increases 30 – 50%  
  - Increase begins as early as 5 weeks
  - 50% of the increase occurs by 8 weeks
  - Increase peaks at about 32 weeks
- CO = HR x SV  
  - Both heart rate and stroke volume increase
- Renal blood flow increases in pregnancy

Dosing Regimens Pregnancy vs Non-pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prophylactic Pregnancy</th>
<th>Prophylactic Non-Pregnancy</th>
<th>Treatment Pregnancy</th>
<th>Treatment Non-pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>enoxaparin</td>
<td>30 mg BID (40 mg QD) *</td>
<td>35 mg BID (40 mg QD)</td>
<td>1 mg/Kg BID **</td>
<td>1 mg/Kg QD or 1.5 mg/Kg QD</td>
</tr>
<tr>
<td>dalteparin</td>
<td>2500 – 5000 IU BID ** (5000 IU QD) *</td>
<td>2500 – 5000 IU QD</td>
<td>100 IU/Kg BID **</td>
<td>100-200 IU/Kg QD ≤10,000 IU/QD</td>
</tr>
</tbody>
</table>

Monitor anti-Factor Xa levels in pregnancy and adjust dose:  
* Prophylaxis: peak 0.2 – 0.4 & trough 0.1 – 0.3 IU/mL  
** Treatment: peak 0.5 – 1.2 & trough 0.2 – 0.4 IU/mL

LMWHs in Pregnancy

- Monitor anti-Factor Xa levels and adjust dose:  
  - Prophylaxis: peak 0.2-0.4 & trough 0.1-0.3 IU/mL  
  - Treatment: peak 0.5-1.2 & trough 0.2-0.4 IU/mL
- Barbour LA (2004) 13 pregnancies on therapeutic dalteparin with initial dose 100 IU/Kg BID  
  - 85% required one or more upward dose titrations  
  - By 30 wks, 50% of women required dalteparin 140 IU/Kg BID to maintain therapeutic anti-Factor Xa levels
Fetal Exposure to LMWH

- Is the fetus exposed to heparins or LMWHs?
  - Yes
  - No
- Molecules > 1000 Daltons do not easily cross the placenta
- Even LMWHs are too large
  LMWHs have mass of 2000-9000 Da
  Unfractionated heparins mean mass 15,000 Da

Lamotrigine

- Lamotrigine is cleared predominantly through which mechanism(s)?
  - A. Metabolized by CYP3A4 and 2C9, and then renally cleared
  - B. Renally cleared as unchanged drug
  - C. Glucuronidated and then renally cleared

Lamotrigine Clearance

- Phase II hepatic metabolism:
  Conjugated via N-glucuronidation
  Followed by renal clearance

- We know renal clearance goes up in pregnancy, but what happens to glucuronidation?
  - A. Goes up
  - B. Goes down
  - C. Stays the same
Lamotrigine in Pregnancy

- Estradiol is a potent inducer of glucuronidation
  UGT 1A family
  *(uridine 5’-diphosphate glucuronosyltransferase)*
  – 1A4 and to a lesser extent 1A3
- Estrogens ↑ clearance of LTG via UGT 1A4
- Even with OCPs & EE, Cl of LTG increases:
  - Sabers 2003:
    - LTG can be reduced by >50% in women on OCPs
  - Reimers 2005:
    - LTG controls 5.6 ± 3.1 mg/L
    - LTG & OCP (EE/P) 2.0 ± 1.3 mg/L
    - LTG & OCP (P only) 5.4 ± 2.1 mg/L

Lamotrigine in Pregnancy

- Fotopoulou, 2009:
  Mean increase in LTG clearance in pregnancy
  – 1st trimester: 197%
  – 2nd trimester: 236%
  – 3rd trimester: 248%
  Mean increase in dosing to maintain pre-LTG levels: 250%
  Cl of LTG back to pre-pregnancy rates by 3 wks pp

Monitoring Lamotrigine in Pregnancy

Establish effective pre-pregnancy LTG level
- Monitor levels every 4 weeks at the same time relative to dosing & adjust LTG dose prn
- Anticipate significant increase in dosing requirements
  - pre-pregnancy LTG 150 mg BID →
  - 3rd trimester 400 mg BID
- Begin taper down by postpartum hospital discharge and recheck levels every few weeks
• Fetal tachyarrhythmias occur in ~ 0.5% of pregnancies

• If untreated and present for an extended period, fetal SVT can lead to fetal cardiac failure, hydrops, and fetal or neonatal demise.
• Digoxin is the primary initial therapy
  – Slows AV transmission and decreases ventricular rate
• Drug to mom with goal to treat infant

• Because digoxin is a medium-sized molecule that easily crosses the placenta, fetal levels are the same as maternal levels.
  – True?
  – False?
Digoxin in Pregnancy

- Very difficult to get therapeutic levels of digoxin in the fetus
  - Umbilical cord digoxin 0.4 ng/mL vs maternal digoxin 3.6 ng/mL
    (King CR, 1984)
  - Fetal (umbilical cord) / Maternal levels: 0.1 to 0.9 with levels frequently < 0.5
    (Syme MR, 2004)

- Why are fetal levels so disproportionately low?
  - A. Placental enzymes metabolize digoxin before reaching the fetus.
  - B. Placental P-glycoprotein actively transports digoxin back into maternal circulation away from the fetus.
  - C. Fetal hepatic enzymes more actively metabolize digoxin, resulting in lower levels.

P-glycoprotein (Pgp)

- MDR1 gene (multi-drug resistance)
- ATP binding cassette transporter – efflux transporter
- Transports chemicals back "out" to the other side
- Binds to a large number of different drugs including digoxin
- Location: intestinal mucosa, liver, kidney, blood-brain barrier, PLACENTA:
  apical brush border – maternal facing
Digoxin in Pregnancy

- 28-32 weeks vs 6-10 weeks postpartum
  - $AUC_{0→48}$: 7.3 ± 1.6 vs 9.3 ± 2.2 ng*h/mL, P<0.006
    - 19% lower in pregnancy
  - $C_l_{renal}$: 181 ± 25 vs 115 ± 25 mL/min, P<0.002
    - 60% greater in pregnancy
    - Good correlation between CrCl and digoxin renal clearance (r=0.8)
  - $C_l_{secretion}$: 73 ± 22 vs 37 ± 14 mL/min, P<0.002
    - 120% greater in pregnancy
  - $f_u$: 67 ± 4 vs 63 ± 5 %, P<0.002
    - 5.8% greater in pregnancy

Digoxin in Pregnancy

- Why is clearance of digoxin increased in pregnancy? All of the following may contribute:
  - Renal P-glycoprotein and organic anion transporter polypeptides (OAT) increase renal secretion
  - Increase in GFR increases renal clearance
  - Increase in unbound digoxin increases clearance

- Dosing of digoxin may need to be greater than non-pregnant expectations in order to adequately treat fetal SVT
- Often need to add second drug: flecainide, sotalol, amiodarone

References

References, cont.

Assessment of Learning
“Medication Dosing in Pregnancy”
Catherine S. Stika, MD

1. Which one of the following statements is NOT true about the use of low molecular weight heparins (LMWHs) in pregnancy?
   a. The volume of distribution of LMWHs increases in pregnancy because total plasma volume increases by about 40%.
   b. LMWHs have to be stopped just prior to anticipated delivery and changed to unfractionated heparin because the smaller molecules of LMWHs can cross the placenta and affect the fetus during birth; whereas, unfractionated heparin does not.
   c. Renal clearance of LMWHs increases in pregnancy beginning as early as 8 wks.
   d. Monitoring anti-Factor Xa levels is critical so that dosing of LMWHs can be adjusted to maintain adequate anti-coagulation.

2. Which one of the following statements is true about the use of lamotrigine in pregnancy?
   a. Lamotrigine undergoes Phase II glucuronidation prior to being renal cleared, both of which are increased in pregnancy.
   b. Lamotrigine undergoes hepatic CYP P450 3A4 metabolism which increases early in the first trimester.
   c. Clearance of lamotrigine increases during pregnancy, but not until late in the 3rd trimester, when the dosing needs to be increased.
   d. Lamotrigine levels need to be checked weekly during pregnancy but the timing of the blood draw is not critical.

3. Which of the following statements is true about the use of digoxin in pregnancy?
   a. Digoxin fetal umbilical to maternal blood levels are close to 1.0, which means that digoxin readily crosses the placenta via passive diffusion.
   b. Digoxin is not a substrate for P-glycoprotein in the placenta, but is affected by P-glycoprotein in the intestines and kidney.
   c. P-glycoprotein and perhaps organic anion transporters (OAT) are both involved in the increased renal secretion of digoxin in pregnancy.
   d. Digoxin is highly effective in converting fetal supraventricular tachycardia back to sinus rhythm.