Pediatric Parenteral Nutrition

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The speaker has no conflict to disclose.

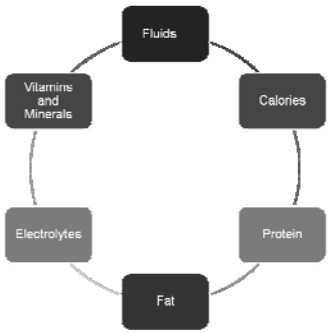
Pediatric Parenteral Nutrition Goals and Objectives

- 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 vomitting or diarrhea
- Hypercatabolic ICU patients
- Patients with short bowel syndrome that cannot meet their needs enterally

Nutritional Goals

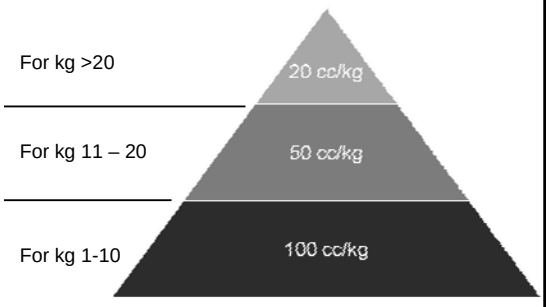


Parenteral Nutrition Access

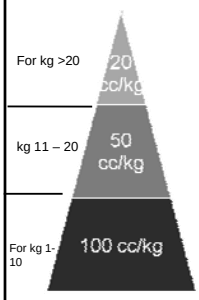
Central Line
- Administer higher osmolarity
- Risk of infection
- Mechanical issues

Peripheral Line
- Not to exceed 900 mOsm/L
  - Max dextrose 10 – 12%
  - Max protein 2.5%
  - Calcium 10 meq/L
  - Potassium 40 meq/L

Fluid Requirements



Ex. Calculate a 15 kg patient's maintenance fluid requirements



Patient's Weight		*Appropriate Dosage*
X	**5 kg**	**250 cc**
		+
X	**10 kg**	**1000 cc**
		1250 cc

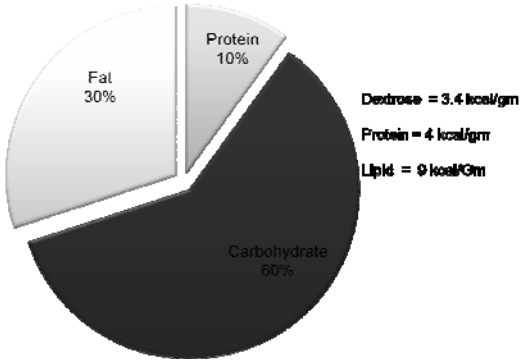
Parenteral Nutrition Order

Patient Weight	1250 gm	15 kg
Line	Central line	Central Line
Volume	125 ml (5.2 ml/hr)	1250 ml (52 ml/hr)
Dextrose		
Protein		
Electrolytes		
• NA		
• K		
• Cl/Acetate		
Phos		
• Ca		
• Mg		
MVI/Trace		
Intralipid		

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

Caloric Distribution



Glucose

Preterm Infants

- Glucose intolerance is common
- Start low and titrate
- Recommended glucose infusion rate (GIR)
  - VLBW to start at 4 – 6 mg/kg/min
  - Lager 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 Dextose 10 – 12.5% and titrate

Glucose Infusion Rate???

- Calculation of Dextrose %

(6 x (**desired GIR)** x wt in kg) ÷ divided by rate in ml/hr = % Dextrose

(6 x (**6**) x 1.25 kg) / 5.2 ml/hr = 8.6%

- Calculate GIR from % Dextrose

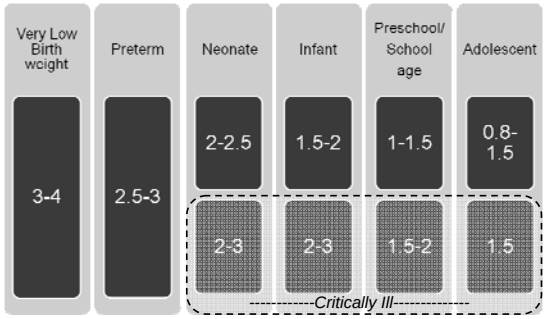
((% dextrose x volume of tpn x 1000) ÷ 1440 min) ÷ wt in kg = mg/kg/min

((0.086 x 125 ml x 1000) ÷ 1440 min) ÷ 1.25 kg = 6 mg/kg/min

Parenteral Nutrition Order

Patient Weight	1250 gm	15 kg
Line	Central line	Central Line
Volume	125 ml (5.2 ml/hr)	1250 ml (52 ml/hr)
Dextrose	8.5%	10% - 12%
Protein		
Electrolytes		
• NA		
• K		
• Cl/Acetate		
Phos		
• Ca		
• Mg		
MVI/Trace		
Intralipid		

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



Amino acid composition

- Enzyme immaturity contributes to conditionally essential amino acids
- Fomulations 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

Parenteral Nutrition Order

Patient Weight	1250 gm	15 kg
Line	Central line	Central Line
Volume	125 ml (5.2 ml/hr)	1250 ml (52 ml/hr)
Dextrose	8.5%	10% - 12%
Protein	2.5% (3.1gm = 2.5 gm/kg/day) Trophamine	1.8% (22.5 gm =1.5 gm/kg/day) Aminosyn
Electrolytes		
• NA		
• K		
• Cl/Acetate		
Phos		
• Ca		
• Mg		
MVI/Trace		
Intralipid	3.6 ml (0.6 gm/kg/day)	96 ml (1.3 gm/kg/day)

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 – 0.5)
  - 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

Parenteral Nutrition Order

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Protein	2.5% (3.1gm = 2.5 gm/kg/day) Trophamine	1.8% (22.5 gm =1.5 gm/kg/day) Aminosyn
Electrolytes		
• NA	2 meq/kg	96 meq (77 meq/l)
• K	none	30 meq
• Cl/Acetate	All acetate	1 meq/kg acetate the rest Cl
Phos	1 – 1.3 mmol/kg	15 mmol
• Ca	2.5 meq/kg	9.2 meq (2 gm)
• Mg	Based on labs	3 meq
MVI/Trace	Standard + x-tra zinc	Standard
Intralipid	3.6 ml (0.6 gm/kg/day)	96 ml (1.3 gm/kg/day)

Parenteral Nutrition Order

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Protein	2.5% (3.1gm = 2.5 gm/kg/day) Trophamine	1.8% (22.5 gm =1.5 gm/kg/day) Aminosyn
Intralipid	3.6 ml (0.6 gm/kg/day)	96 ml (1.3 gm/kg/day)
Calories	43.3 non protein k/cal	617 non protein k/cal
Calories/kg/day	35 kcal/kg/day	41 kcal/kg/day

References

- A.S.P.E.N. Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN 2002; 26 (1, Suppl.): 1SA-138SA.
- A.S.P.E.N. Board of Directors and the Clinical Guidelines Task Force. Nutrition Support of the Critically Ill Child. JPEN 2009; 33;260 – 275.
- Hak EB, Helms RA. Textbook of therapeutics: drug and disease management. 8th ed. Philadelphia: Lippincott Williams & Wilkins;c2006. Chapter 16, Pediatric Nutrition Support; p. 340 – 366.
- Shulman RJ, Phillips S. Parenteral nutrition in infants and children. Journal of Pediatric Gastroenterology and Nutrition. 2003, 36: 587-607

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

Pediatric Sedation in the ICU

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Speaker has not conflict of interest to disclose

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

Drug	Dosing
Morphine sulfate	0.1mg/kg q3-6h Neonates: 0.05 mg/kg q1-6h
Hydromorphone (Dilaudid®)	0.015 mg/kg q3 - 6h
Fentanyl (Sublimaze®)	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)
Methadone (Dolophine®)	0.1- 0.2 mg/kg q 6-8h

Opiates

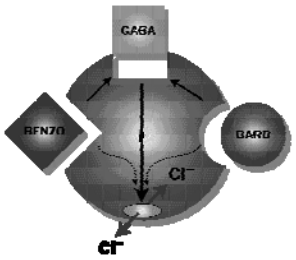
Physical tolerance to opiates develops with time, especially with fentanyl. There is no absolute "maximum" dose of opiates. Some patients may require 5-10 times the "recommended" dose due to the tolerance, which develops over time.

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, synpathomimetic 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 halluciantions and emergence reactions with low-dose barbiturate or bonzodiazepine

Anesthetics – Ketamine

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
Gasping 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 Dexmeditomine

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

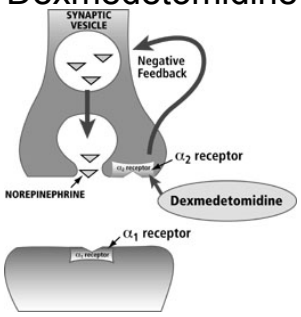
Dexmedetomidine

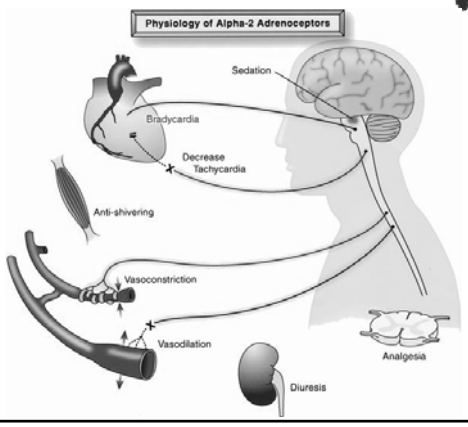
Mechanism of Action

– 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





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)

- Tobias JD, Berkenbosch JW. South Med J 2004;97:451-5.

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.

Mason KP et al.,Paediatr Anaesth. 2008 May;18(5):403-11 and Mason KP, et al.Paediatr Anaesth. 2008 May;18(5):393-402

Dexmedetomidine

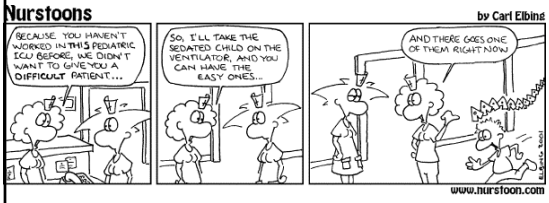
Iatrogenic Opiate and Benzodiazepine Withdrawal

- Retrospective study; 7 infants : 3 to 24 months of age
- Continuous fentanyl infusion, supplemented with midazolam
- Withdrawal documented via Finnegan score > or = 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

Reference	Procedures	Drug regimen: Propofol (P) Ketamine(K) Fentanyl(F) Midazolam (M)	Apnea (%)	HypoTN < Fifth% (%)	Halluc. Agitation (%)	Overall adverse effects requiring intervention (%)	Comments
Vardi	BMA,TEE,LP,Peg, IT inj, IA inj, CL, B, W	**P** 2.5mg/kg + 200 mcg/kg/min	17	10	0	45	
	BMA,TEE,LP,Peg, IT inj, IA inj, CL, B, W	**M** 0.1mg/kg + **K** 2 mg/kg + **F** 2 mcg/kg	6	4	11	23	1 pt required intubation
Bassett	(ER) Fractures, burns	**P** 1 mg/kg + 0.5mg/kg + **F** 1mcg/kg	5	25			Bradycardia 6%
Parker	LP, BMA, R, I	**M** 0.05-0.1 mg/kg + **K** 1-2mg/kg	14		7		30% imaging (non-painful) procedures; oral secretions significant
Hertzog	LP, IT, BMA, CL, E,TEE	**P** 1.8mg/kg (max 8.8mg/kg)	6	50		67	Myoclonus in 3.6%

BMA-Bone marrow aspiration, TEE transesophageal echocardiogram, LP- Lumbar puncture, Peg-Peg tube placement, IT-intrathecal injection, IA-intra-articular steroid injection, CI-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. (60 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, O_2 saturation, and RR
- Results:
  - P and D equally effective is 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)

State Behavioral Scale (SBS)[1]
Score as patient's response to voice then touch then noxious stimuli
(Planned ETT suctioning or <5 seconds of nail bed pressure)

Score	Description	Definition
-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 oonsole 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 (WAT-1)

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier													
	Date:												
	Time:												
Information from patient record, previous 12 hours													
Any loose /watery stools	No = 0 Yes = 1												
Any vomiting/wretching/gagging	No = 0 Yes = 1												
Temperature > 37.8°C	No = 0 Yes = 1												
2 minute pre-stimulus observation													
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1												
Tremor	None/mild = 0 Moderate/severe = 1												
Any sweating	No = 0 Yes = 1												
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1												
Yawning or sneezing	None or 1 = 0 ≥2 = 1												
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 (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2												
Total Score (0-12)													

"You can't just switch them. If your wife asked you to change the baby, she probably meant the diaper."

State Behavioral Scale (SBS)[1]
Score as patient's response to voice then touch then noxious stimuli
(Planned ETT suctioning or <5 seconds of nail bed pressure)

Score	Description	Definition
-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)

Patient Identifier														
	Date:													
	Time:													
Information from patient record, previous 12 hours														
Any loose /watery stools	No = 0 Yes = 1													
Any vomiting/wretching/gagging	No = 0 Yes = 1													
Temperature > 37.8°C	No = 0 Yes = 1													
2 minute pre-stimulus observation														
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1													
Tremor	None/mild = 0 Moderate/severe = 1													
Any sweating	No = 0 Yes = 1													
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1													
Yawning or sneezing	None or 1 = 0 ≥2 = 1													
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 (SBS[1] ≤ 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 SBS[1] at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS[1] 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.

2 minute pre-stimulus observation:

- ✓ **State**: Score 1 if awake and distress (SBS[1]: ≥ +1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative (SBS[1] ≤ 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 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** (SBS[1] ≤ 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).

[1]Curley et al. State behavioral scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2006;7(2):107-114.

Sedation in the ICU/NICU Post-test – Chris Steffensen ACMC Hope Children's Hospital

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 "gasping 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

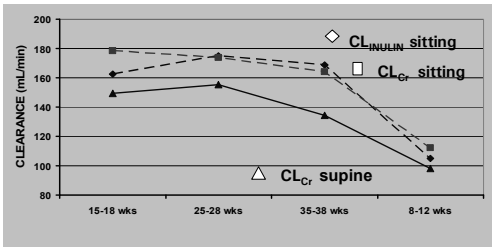
Plasma Volume Expansion

- 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



Davison JM, et al. Br J Obstet Gynaecol Br Commonw 1974;81:588-95.

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

Medication	Prophylactic Pregnancy	Prophylactic Non-Pregnancy	Treatment Pregnancy	Treatment Non-pregnancy
enoxaparin	30 mg BID * (40 mg QD) *	30 mg BID (40 mg QD)	1 mg/Kg BID **	1 mg/Kg QD or 1.5 mg/Kg QD
dalteparin	2500 – 5000 IU BID * (5000 IU QD) *	2500 – 5000 IU QD	100 IU/Kg BID**	100-200 IU/Kg QD ≤18,000 IU/d

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

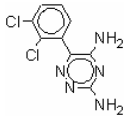
- Is the fetus exposed to heparins or LMWHs?
  - Yes
  - No
- Molecules > 1000 Daltons do not easily cross the placenta
- Even LMWHs are too large
  LMWHs have mass of 2000-9000 Da
  unfractionated heparins mean mass 15,000 Da

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



Lamotrigine

- 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

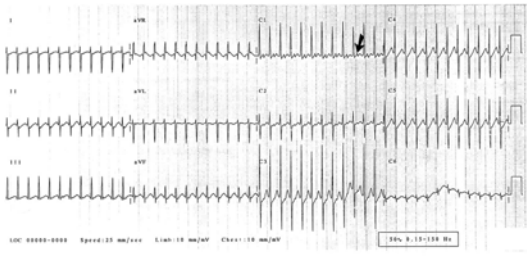
Monitoring Lamotrigine in Pregnancy

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

Digoxin in Pregnancy

- Fetal tachyarrythmias occur in ~ 0.5% of pregnancies



Digoxin in Pregnancy

- 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

Digoxin in Pregnancy

- 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

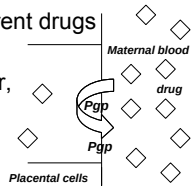
- Very difficult to get therapeutic levels of digoxin in the fetus
  - Umbilical cord digoxin 0.4 ng/mL vs maternal digoxin 3.6 ng/mL *(King CR, 1984)*
  - Fetal (umbilical cord) / Maternal levels: 0.1 to 0.9 with levels frequently < 0.5 *(Syme MR, 2004)*

Digoxin in Pregnancy

- 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
  Digoxin 0.25 mg po (*Hebert, M 2008)*
  - $AUC_{0\rightarrow48}$ 7.3 ± 1.6 vs 9.3 ± 2.2 ng*h/mL P<0.006
    19% lower in pregnancy
  - Cl_{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)
  - $Cl_{secretion}$ 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, sotatol, amiodarone

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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.