Drug Shortages with Parenteral Nutrition

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Conflict of Interest
None

Objectives
1. Discuss potential stability/compatibility issues when changing between products or combining products for nutrition support during a shortage
2. Formulate a shortage “protocol” or substitution policy for use during a shortage of parenteral nutrition components
3. Discuss effects of shortages on transition of care for patient’s receiving parenteral nutrition

Assessment Question
Which of the following statements would be appropriate to include in a policy for management of drug shortages?
A. Guidelines for rationing or restricting use of a product are approved by the P&T committee.
B. Individual physicians have sole discretion for use of a product in short supply after having acknowledged rationing guidelines.
C. The pharmaceutical buyer will secure several months supply of a drug as soon as there is a hint of an upcoming shortage.
D. All drugs in short supply will require prior approval of the section chief prior to dispensing from pharmacy.

Drug Shortage Policy: UHC Hospitals and Clinics


I. PURPOSE:

II. DEFINITIONS:

III. POLICY:
A. The Drug Information Service (DIS), under the auspices of the Pharmacy and Therapeutics Committee, is responsible for investigating and providing information about potential drug shortages that may affect patients at University Hospital and Clinics. The Pharmacy and Therapeutics Committee approves any plans for restricting use or rationing limited supplies.

Am J Health Syst Pharm. 2003;60:245-253
Am J Health Syst Pharm. 2009;66:1399-1406
Drug Shortage Policy (cont.)

IV. PROCEDURE:
D. Identify available inventory and usual use patterns
E. Develop a management strategy
F. P&T approves decisions to ration or restrict product
G. Notify Pharmacy personnel, the P&T Committee, and affected clinicians about drug shortages via e-mail [and other media]

4. Rationing or restriction strategies
5. Specific management strategies
6. Recommendations for alternative agents if appropriate


Shortages with Parenteral Nutrition

- Macronutrients
  - Amino acids
  - IVFE
  - Dextrose – 25% and 50%
- Micronutrients
  - Electrolytes
  - Cysteine
  - Multivitamin
  - Trace elements – individual and multi-trace products
  - Carnitine

Assessment Question:
Which of the following would be an appropriate method of managing a shortage of IV multivitamin?

A. Allow the large stock of pediatric IV multivitamin to be used in adults until that stock is depleted.
B. Continue adding 10 ml MVI daily to all adult PN formulations since your pharmaceutical buyer can obtain MVI via the gray market.
C. Hold MVI for all adult patients and reserve available stock for pediatric patients and adults on PN over 4 weeks.
D. Restrict MVI to patients with severe malnutrition or those on PN over 2 weeks and provide thiamine in PN for all other patients.

Shortage Management: Substitute Product – Amino Acids

Standard amino acid solutions
- FreAmine, Travasol, Aminosyn, Aminosyn II
- Therapeutic equivalents
  - Equal efficacy as protein source
- Not generic equivalents
  - Vary in pH
  - Phosphate content
  - Grams of individual AA vary

Shortage Management: Substitute Product – Amino Acids

- FreAmine, Travasol, Aminosyn II
  - Acceptable for 3-in-1
  - Aminosyn pH is too low for 3-in-1
- FreAmine
  - Contains phosphate
  - Calcium-phosphate solubility affected
  - Higher pH than other AA solutions
  - Higher acetate content

Influence of pH on Solubility of Calcium-Phosphate

Am J Hosp Pharm 1982; 39:49
Influence of Amino Acid Brand on Calcium-Phosphate Solubility

Dextrose 20% with Amino Acids 2%
Aminosyn (—)
Travasol (- - -)
FreAmine (-----)

Trave's Calcium and Phosphate Compatibility in Parenteral Nutrition, 2001

Shortage Management: Substitute Products – IV Fat Emulsion

- Intralipid, Liposyn, Clinolipid
- Therapeutic equivalents (???)
  - All contain egg phospholipid and soybean oil
  - All prevent EFAD
  - Minimal dose (g/day) to prevent EFAD varies
- Not generic equivalents
  - Different fatty acid composition
  - Stability as 3-in-1 may vary

Shortage Management: Ration/Restrict Use – Amino Acids

- Follow criteria established for PN eligibility
- Is the GI tract functional?
- Is GI tract access feasible?
- How long has the patient been without adequate nutrition?
- What is the risk of malnutrition?
- Start AA at lowest acceptable amount per assessment
- Re-assess AA requirement weekly and adjust if appropriate
- Use commercial PN formulation
  - Compromise calories, protein or fluid (?)

Shortage Management: Substitute Products – IV Fat Emulsion

Available IV Fat Emulsions
- Intralipid, Liposyn, Clinolipid
  - Fat source affects fatty acid profile
    - Intralipid and Liposyn III: Soybean oil
    - Liposyn II: Soybean oil + Safflower oil (1:1 ratio)
    - Discontinued Feb 2014 due to shortage of raw product
    - Clinolipid: Soybean oil + Olive oil (1:4 ratio)
  - 10%, 20%, or 30% emulsion
  - Different clearance rates
  - Approved uses differ

IV Fat Emulsion

- “Today’s approval of Clinolipid will help in the effort to resolve this shortage [injectable lipid emulsion] so that patients have access to these parenteral nutrition products.”
  - Donna Griebel, M.D., director of the Division of Gastroenterology and Inborn Errors Products in the FDA’s Center for Drug Evaluation and Research.
  - October 3, 2013

- Same manufacturer as Intralipid
- For adults – not for preterm infants or pediatrics
- Only available in 1 Liter bag
- Olive oil contains less EFAs
  - Linoleic acid (C18:2w6): 8% vs 50% in soy
  - Alpha-linolenic acid (C18:3w3): Trace vs 7% in soy
Shortage Management: Ration/Restrict Use – IVF E

- Delay start of IVF E
- Risk of EFAD
- High Risk Populations
  - Neonates
  - Pediatric patients
  - Short bowel syndrome
  - Severe fat malabsorption
    - Pancreatic enzyme therapy trial

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Shortage Management: Substitute Products – Calcium

Calcium salts (intravenous)
- Calcium gluconate, calcium chloride
- Therapeutic equivalent
  - Equal physiologic effect with equal mEq Ca dose
- Not generic equivalents and not interchangeable in PN
  - Different dissociation characteristics
    - Precipitation risk with phosphate
    - Risk of vascular damage if extravasation
    - Minimal data with CaCl₂ on calcium-phosphate solubility in PN

Example:
- Phosphate
- Sodium Phosphate Concentration (mmol/L)
- Calcium Concentration (mEq/L)

Phosphate Salts (intravenous)
- Potassium phos, sodium phos, sodium glycerol phos
- Therapeutic equivalent
  - Equal physiologic effect with equal mMol phosphate dose
- Not generic equivalents
  - Cation differences
    - 35 mMol P = 51 mEq K, 47 mEq Na vs 70 mEq Na for sodium glycerol phos
  - Different dissociation characteristics
  - Precipitation risk with calcium differs for sodium glycerol phos

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Shortage Management: Substitute Products – IV Multivitamins

- Multivitamin injectable (MVI) products
  - Adult products
  - Pediatric products
- Individual vitamin products
  - Thiamine – most critical
  - Ascorbic acid, folate, pyridoxine, vitamin B12 available in parenteral form
- Delay start of MVI
  - Reduced dose daily vs full dose 2-3 days weekly
- Use oral product when ever possible

Example:
- Phosphate
- Sodium Phosphate Concentration (mmol/L)
- Calcium Concentration (mEq/L)
Shortage Management: Substitute Products – Trace Elements

- Multi-trace element products
- Adult products
- Pediatric products
- Neonatal products
- Individual trace element products
- Imported products differ from US products
  - Dose
  - Content

Differences in imported vs US products
- Content
  - Pediatric – selenium 2 mcg/kg in 1 mL dose; no chromium
  - Adult
    - Zinc and copper as chloride salts
    - Ferric chloride 0.11 mg/dose → clinical and stability issues
    - Molybdenum, iodine, fluorine included
- Doses
  - Pediatric – 1 mL/kg
  - Adult – 10 mL single dose plastic ampule

Recommended IV Intake of ZINC in mcg/kg/day:

<table>
<thead>
<tr>
<th>ZINC</th>
<th>ATLE a.Peds</th>
<th>ATLE Neonatal</th>
<th>Kabi Pediatric</th>
<th>MTE 4 or 5 Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in mL/kg</td>
<td>0.2</td>
<td>0.2</td>
<td>1.0</td>
<td>Pediatric dose: 0.025</td>
</tr>
<tr>
<td>Amount in mcg/kg per dose</td>
<td>0.2 x 100 mcg/kg</td>
<td>0.15 x 250 mcg/kg</td>
<td>0.125 x 350 mcg/kg</td>
<td></td>
</tr>
</tbody>
</table>

Infants: Premie up to 3 kg: 400 Neonate (Term): 250
Premie (3–3 kg): 450 – 500 < 3 months: 250 mcg/kg/day
Over 3 months: 50 mcg/kg/day (maximum 5,000 mcg/day)
Child (10–40 kg): 50–125 (maximum 5,000 mcg/day)

Zinc deficiency dermatitis: bullous and erosive lesions
- At risk populations
  - Premature neonates:
    - Require zinc 400 mcg/kg/d
  - Increased losses via GI tract:
    - Short gut syndrome
    - GVHD of GI tract
  - High output EC fistulas

http://www.cdc.gov/mmwr
Photo/S.A. Norton, Children’s National Medical Center, Washington, DC
Transition of Care

- PN safety issues
  - PN made for BUD of 9 days vs 30 hr in pt
  - Change of components → stability may be compromised
- Patient’s ability to manage PN
  - Frequent changes in PN regimen for home additives
  - Separate infusions of micronutrients
    - Increased fluid
    - More time to complete regimen
    - Increased entry into vascular access device → infection risk
    - Increased cost since not part of PN

Assessment Question:
Which is the most appropriate method for restricting IV multivitamin use in home PN patients dependent on PN for more than a year?

A. Have pharmacy add 4 mL adult MVI from a bulk bottle to each PN bag when compounded.
B. Have the patient add a full 10 mL dose of adult MVI 3 times weekly just before hanging their PN.
C. Add thiamine to each bag of PN during compounding and ask the patient to take an oral multivitamin daily.
D. Omit MVI until the shortage resolves and ask the patient to take an oral multivitamin daily.

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