What Do You Mean We Are Out of That Drug? The Drug Shortage Problem in the NICU

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The speaker has disclosed that she is a pharmacology column editor for Neonatal Network. This affiliation could be perceived as having a bearing on the subject matter of her presentation. She has no significant financial interest or relationship with any other companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

During this session the speaker will review the recurring and current drug shortage problem in the NICU, identify the causes of the drug shortage problem, the impact on patient care, and efforts to resolve the problem.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- identify contributing factors leading to sterile injectable drug shortages;
- recognize the drugs commonly used in NICU that have been on the Drug Shortage List;
- list the patient care impact of drug shortages.

References


U.S. Food and Drug Administration. *How drugs are developed and approved.* Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm


Session Outline

See presentation handout on the following pages.
Drugs are out of that drug?
Review of Drug Shortage Problem in the NICU
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For FANNP

Current Shortage “worst in 30 years
• Affecting drugs central to inpatient treatment programs
• Large populations of patients affected
• 2011 shortages 360–600% higher than 2006
• Generic drugs involving demand vs. supply
• 70% of prescription drugs are generic

Primary Causes of Drug Shortage

Causes of Drug Shortage

Depleted raw materials
• Depleted rare materials
• Rate–limited production
• Discontinuation of manufacturing
• Deliberate corporate decisions to discontinue
• Regulatory issues, voluntary recalls
• Generic drug profit reduction

Dynamics of Sterile Injectable Drug Shortages

Critical Drug Shortages
Percentage of Hospitals experiencing drug shortages by treatment categories

Source: 2011 analysis of survey data from 820 hospitals, collected over a six-month period ending June 2011
**Recent Critical Drug Shortages**
- Sodium
- Thiopental
- Succinylcholine
- Propofol
- Furosemide
- Doxycycline
- INH
- Epinephrine
- Heparin
- Morphine
- 50% dextrose
- Potassium Acetate

**Drug Shortages in Neonatal and Pediatrics**
- 0.5% Erythromycin ophthalmic ointment
- Calcium gluconate
- Potassium chloride
- Selenium
- Intravenous Lipid Emulsion
- Potassium acetate
- Heparin
- Rocuronium
- Morphine
- Midazolam
- Diazepam
- Atropine
- Digoxin
- Dopamine
- Lidocaine
- Amikacin
- Methotrexate

**NICU Specific Drug Shortages**
- Midazolam
- Ibuprofen
- Amikacin
- Atropine
- Fentanyl
- Naloxone
- Indomethacin
- Prostaglandin E1
- Dexamethasone
- TPN Additives
  - 50% dextrose
  - Calcium gluconate
  - Potassium chloride
  - Potassium acetate
  - Selenium
  - Heparin
  - Potassium phosphate
  - Magnesium sulfate
  - Zinc
  - Trace elements

**Cancer Drug Shortages**
- Pediatric Cancers
  - Methotrexate
  - Leukemia
  - Osteosarcoma
- Breast Cancer
  - Doxil
  - Myeloid Leukemia
  - Cytarabine
- Stockpiled drugs costing &800–$900/gm vs $16

**Process of Drug Development**
- Patent protection
  - Proprietary production
  - Market exclusivity
  - Repay cost of R&D
  - Elevate cost to consumer
  - Patent rights 20 yrs
  - Exclusivity rights
  - 180 days to 7 yrs
- Patent expiration
  - Generic production
  - Bioequivalent
  - Cost reduction
  - Reduced profit
  - Reduced manufacturing incentives
  - Limited manufacturers

**Steps in Drug Manufacturing**
1. **Ingredients**
2. **Manufacture**
3. **Packaging**
4. **Shipping**
5. **Storage**
### Characterization of Drugs In Short Supply

<table>
<thead>
<tr>
<th>Form Type</th>
<th>Brand–Generic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectables</td>
<td>15%</td>
</tr>
<tr>
<td>Orals</td>
<td>1%</td>
</tr>
<tr>
<td>Inserts/Implants</td>
<td>11%</td>
</tr>
<tr>
<td>Rectals/Topicals</td>
<td>4%</td>
</tr>
<tr>
<td>Dermatologics</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Generic Drug Manufacturing Issues
- Limited operating revenues
- Vulnerable to supply and demand inequities and limitations
- Tend to meet demands for high-volume drugs
- Reduce production of high cost low-volume drugs
- Time to establish production lines lead to delays

### Large Generic Pharmaceutical Manufactures in USA
- Akorn Pharmaceuticals
- APP Pharmaceuticals (Div. of Fresenius Kabi)
- Bedford
- Ferring Pharmaceuticals, Inc.
- Hospira Inc.
- Mylan Institutional
- Teva Pharmaceuticals (largest)
- West–Ward Pharmaceuticals

### Cost Difference Brand vs. Generic Drugs
- On average, the cost of a generic drug is 80 to 85 percent lower than the brand name product.
- 8 in 10 prescriptions filled in the United States are for generic drugs.
- 2010 the use of FDA-approved generics saved $158 billion.
  - An average of $3 billion every week.
- Generic manufacturers sell at lower prices.
  - Not required to repeat the costly clinical trials of new drugs.
  - Generally do not pay for costly advertising, marketing, and promotion.

### Branded Generics
- Bioequivalent drugs post patent protection manufactured by Brand Pharmaceutical Manufacturers (GlaxoSmithKline, Pfizer, etc).
- Largest outside of US and UK.
  - Until recently, many brand-name drug makers invested the bulk of their research and marketing dollars in the development of blockbuster drugs, only to cede their intellectual property and market share to lower-priced generic competitors once patents expired. But now, with an estimated $89 billion in brand-name drug sales in the United States at risk to generic competition over the next five years, according to IMS Health, some drug makers are selling generics to offset revenue declines— as well as wringing some post-patent profits from the innovative drugs they developed.
**Branded Firm Efforts to Extend Patent Protections**

- Delay in generics increase profits >$12mil/yr
- Introduce new form of drug = 3 yrs of protection
  - More if the new product is re-patented
- Establish secondary patent on production process or drug components
- Challenge a generic firm’s application with FDA
  - Question the bio-equivalence to branded drug
- Acquire rival producers of the raw ingredient
- Introduce branded generic or authorized generic
  - Canada 25% of all generic sales are branded generics
  - Reduce potential generic firms from ANDA application

**Who is Really to Blame**

- Medicare & Medicaid restricted reimbursement
- FDA strict inspections and delayed response
  - Requiring sterility and lack of contamination
- Generic manufacturers weigh eliminating expensive product lines vs. expensive upgrading

**Drug Shortages by Category**

- Injectables
- Dermal/Transdermal
- Inhalation
- Suspension/Solution
- Tablet/Capsule
- Other

**Drug Shortage Impacts on Patient Care**

- Patient treatment delayed
- Patient received less effective drug
- Patient did not receive recommended treatment
- Patient experienced an adverse outcome

Source: American Hospital Association analysis of survey data from 800 nonfederal, short-term acute hospitals collected in 2011.

**Actions & Recommendations**

- Request manufacturer to provide early warning of shortages (legislation to enforce)
- Timely notification of potential drug shortages to industry
- Maintain database of shortages (for professionals and public)
- Prevent and mitigate
  - 2010 efforts prevented 38 shortages
  - 2011 efforts prevented 195 shortages
  - 2012 estimated 200 shortages prevented
- Develop models for prevention

**Hospital Response to Drug Shortages**

- Establish Pharmacy Plan
- Hoarding drugs
- Gray market alternatives (Marked up >5000%) Compounding suppliers
- Cost to hospitals $200 million annually
- Adverse patient outcomes due to delayed treatment and medication errors
Facilities Respond to Drug Shortages

- ~75% had conservation measures placed on drugs.
- ~73% had large, single-dose vials as the only size of drug available.
- 68.2% had to modify the anesthesia technique or management of hemodynamic changes.
- 57.5% had to use a pharmacy to prepare smaller, single-dose syringes which is troubling given all the recent compounding pharmacy scares.
- 45.6% said they themselves prepared smaller, single-dose syringes.
- 21.7% had delayed emergency or recovery.

Issues with Proposed Solutions

- Exporting drugs from other countries
  - FDA controls limit
  - Political and trade issues
  - Other countries resist trades of specific drugs
  - Raw materials from some countries may be contaminated
- Executive Order
  - Expedite approval of new alternative drugs
  - FDA cannot mandate manufacturers to produce
  - New manufacturers take time to commence production

Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012

- Broadened scope of early notification requirement
- Require notice of discontinuance temporary or permanent
- Mandatory reporting of shortages of biological products
- Expedite inspections to mitigate or prevent shortages
- Maintain publically available shortage list including cause and estimated duration

Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012

- Exercise enforcement discretion, in rare instances, for the temporary foreign import of a product in shortage
- Exercise enforcement discretion in appropriate circumstances to permit the distribution of a product in shortage
  - for example by allowing a product with particulate matter to be distributed with the use of a filter to eliminate the particulates

Number of Drug Shortages by Year

Source: FDA.gov

New Drug Shortages 2010-2012

- 2010: 178 drug shortages reported to the U.S. FDA
  - 132 sterile injectable drugs
- 2011: 251 drug shortages reported
  - 183 sterile injectable drugs
- 2012: 117 new drug shortages
  - 84 sterile injectable drugs.
  - Fewer reported new drug shortages.
  - FDA continues to see shortages involving older sterile injectable drugs.
  - cancer drugs,
  - anesthetics used for patients undergoing surgery
  - drugs needed for emergency medicine
  - electrolytes needed for patients on IV feeding TPN
Prevention of Drug Shortages

- FDA has also been able to prevent a significant number of drug shortages
- 2011: Prevented 195 drug shortages
- 2012: Prevented 282 drug shortages
- FDA drug shortage preventions facilitated by increased early notifications from manufacturers.