Management of Drug Shortages

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- Upon completion of this activity, the participant should be able to:
  - Examine the impact of drug shortages on a hospital pharmacy
  - Discuss recent shortage-related legislation
  - Compare available resources for shortage management
  - Identify actions to manage and mitigate drug shortages

Background

- Kuehn BM. JAMA. 2013 Feb 13; 309(6).
Background

- Medications vulnerable to shortages
  - Generics
  - Injectables
  - Oncology
  - Electrolytes
  - Sole-source medications with decreased demand

Impact of drug shortages

<table>
<thead>
<tr>
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<th>% Institutions</th>
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<tbody>
<tr>
<td>Increased doses</td>
<td></td>
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<tr>
<td>Increased cost</td>
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<tr>
<td>Increased frustration</td>
<td></td>
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<tr>
<td>Changed practice</td>
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<td>Compromised care</td>
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Effects of Medication Shortages

- Survey data
  - All affected, directors opinion of impact
- Financial impact
  - 92% report increased drug costs
    - Impact difficult to calculate
  - Annual cost to national healthcare system
    - Purchasing: $200 million
    - Labor: $216 million

Effects of Medication Shortages

- Patient care compromised
  - Treatment delays (82%)
  - Less effective medication (69%)
  - Adverse outcomes (35%)
  - Medication errors (25%)
- ISMP survey: impact on patient care
  - Delays of chemo, procedures
  - Epinephrine error
  - Propofol

Impact at Shands Jacksonville Medical Center

- Quantify impact of shortages at our institution
  - Compared expenses for medications on shortage in 2011 and acceptable therapeutic alternatives to expenses in 2010
  - Searched medication error reports involving medications on shortage and alternatives

Impact at Shands Jacksonville

<table>
<thead>
<tr>
<th>Total expenses by year</th>
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<tbody>
<tr>
<td>2010 expenses</td>
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<tr>
<td>$283,566</td>
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<tr>
<td>$1,577,253</td>
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<tr>
<td>$800,000</td>
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<td>$600,000</td>
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<td>$400,000</td>
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<td>$200,000</td>
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Impact at Shands Jacksonville

Medications contributing most to $283,566 in increased expenditures during 2011

- Cisatracurium
- Diphenhydramine
- Fosphenytoin
- Labetalol
- Desmopressin
- Hydralazine
- Acetylcysteine
- Indomethacin
- Norepinephrine
- Phenylephrine
- Other

Impact at Shands Jacksonville

- 7 errors caused by shortages
  - Expired drug
  - Vasopressin drip
  - Incorrect doses given
    - Phenylephrine concentration changes
    - 10x dose infused twice
  - Delays of care secondary to process change
    - 2 neonatal vitamin K
    - 2 lorazepam IV for seizing patient

Impact at Shands Jacksonville

- Underestimates shortage impact
  - Financial impact
    - Did not include medications as on shortage if were easily able to substitute another product
    - Did not include many chemotherapeutics
    - Does not include labor expenses
      - Estimated 5 hours weekly in committee meetings
      - Did not estimate other labor
  - Patient care impact
    - Relied on voluntary reporting
    - Not reporting expected impacts

Why do shortages occur?

- Little resiliency in supply chain
- Manufacturing Issues
  - Forecasts
  - Formulations
  - Production
  - Quality issues
- Drug Shortage
- Supply Chain Issues
  - Supply Disruption
- Contributing Factors

Causes of shortages

- Multiple potential causes
  - Natural disaster
  - Raw materials
  - Increased demand
  - Inventory practices
  - Regulatory issues
  - Decreased demand → product suspended
  - Manufacturing issues/quality problems
Inventory practices

• Just-in-time inventory

• Inventory changes in setting of shortage
  – Hoarding
  – Stockpiling

Regulatory issues - MMA

• Medicare Modernization Act 2005 (MMA)
  – Changed reimbursement in outpatient setting
  – Erodes selling prices
  – Lower profit margins
  – No incentive to expand or continue production
    • May choose to discontinue product in favor or more profitable line
    • New manufacturers disinterested in producing generics

Regulatory issues - Unapproved drugs

• FDA increased enforcement of Unapproved Drugs
• 1938: Food Drug and Cosmetic Act (FDCA)
  – Pre-1938 = grandfathered, no NDA required
  – FDCA required safety evidence
• 1962: Kefauver Harris Amendment
  – Required safety and efficacy evidence
  – Drugs approved 1938 – 1962 reviewed for efficacy
• FDA requests NDAs for any unapproved drugs
  – Believes few entitled to grandfather clause

Unapproved drugs

Regulatory and manufacturing quality issues

• New FDA Commissioner in 2009
• Enforcement and regulatory activities spiked 2009 – 2011
• Warning letters to manufacturers re: quality increased 42% in 2009 and 156% in 2010

FDA Warning letters 2004-2011
Reported reasons for sterile injectable drug shortages in 2011

Economic drivers of manufacturing quality problems

FDA helps

- Foreign equivalents
  - Propoven from UK for propofol shortage
  - Phenylephrine from UK
  - Sodium bicarbonate
- Allow affected drug with conditions
  - Potassium phosphate – double filtration required
  - Mannitol – heat to dissolve crystals
  - Alteplase 2 mL – suggests filtering

FDA Safety and Innovation Act (FDASIA)

- Executive presidential order – October 2011
- FDASIA – July 2012
  - Provides steady, reliable funding for timely FDA reviews of safety and efficacy
- FDASIA: Title X – Drug Shortages
  - Improved capacity to prevent and mitigate shortages

FDASIA: Title X

- Manufacturers must notify FDA of production interruptions
  - Broadened definition of what must reported
  - Timing requirements
    - 6 months if anticipated
    - ASAP if unforeseen
    - “Failure letter”
ASHP Drug Shortage website
www.ashp.org/DrugShortages

- Managed by the University of Utah Drug Information Center
- Report a new shortage
- Guidelines and resources
- Shortage reports
  - Current
  - Resolved
  - Unavailable medications

FDA website
www.fda.gov/Drugs/DrugSafety/DrugShortages

- Includes information provided by manufacturers
- Shortage reports
  - Current
  - Resolved
  - To be discontinued
- Email notification option
- References ASHP frequently
**Prepare**

- Define the process
  - Who will oversee drug shortage management?
  - Who are the key players?
- Drug Shortage Committee

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**Drug Shortage Committee**

- Composition/Representation
  - Purchasing
  - Therapeutic policy management
  - Central operations
  - Clinical pharmacists
- Acts quickly, proactively
- Long-term monitoring
- Weekly

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**Drug Shortage Committee**

- Gather information
  - Severity of shortage
  - Contact alternative suppliers
  - How are others managing shortages?
- Implement necessary changes
  - Collaborate with affected prescribers
  - Recommend changes appropriate committees
- Orchestrate technology and dispensing changes
- Communicate changes
- When to take "off shortage"?

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**Prepare: Drug Shortage Committee Responsibility flow chart**

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**Prepare**

- Communication plan
  - What are the most effective means to communicate changes?
- Identify management strategies

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**Shortage management strategies**

- Borrow
- Buy off-contract
- Centralize supply
- Change product concentration or size

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Shortage management strategies

- Gray distributors
- Alternate vendors
  - Gather documentation
  - Proper licensing
  - Ask for quality documentation
- Determine level of compounding
  - Sterile to sterile
  - Non-sterile to sterile
- Report problems
- In-house compounding

Critical Shortage of IV Dexamethasone

Therapeutic substitutions
- Vasopressor shortage
- Meropenem shortage
- Labetalol shortage
- Ranitidine shortage
- Dexamethasone

Limit use
- Electrolyte shortages
- Sodium bicarbonate shortage
- Acetylcysteine shortage

Identify

- Becoming aware of a shortage
  - Buyer
  - Engage Central Pharmacy staff
  - Wholesaler
  - Shortage websites
    - Proactively monitor

Operational assessment

- Shortage details
- Stock on hand
- Typical usage
- Alternative product available?
  - Quantity on hand
  - Supply available

Therapeutic assessment

- Patient population affected
- Identify therapeutic alternatives
  - Need for approvals
- Consider impact of limiting use

Assess impact on patient care

- Process changes
  - Prescribing
  - Preparation
  - Distribution
  - Administration
- Management strategies
  - Centralize stock
  - Alternatives
  - Conservation
- Therapeutic difference
  - Efficacy
  - Safety
  - Monitoring
- Safety concerns
  - Errors
  - Delays
  - Administration

Safety concerns

- Same drug, different form or packaging
- Change in concentration or volume
- Similar packaging
- Storage differences
- Different medication (therapeutic substitution)
- Crash carts, emergency trays
Same Drug Different Dosage Form

Same drug & concentration, different volume

Similar Packaging

• Morphine shortage
  – 2 mg & 4 mg syringes
  – Only 5 mg vials available

• Hydromorphone vials have similar packaging to morphine vials

Compounding: same drug, different label & storage

• Dextrose 50% 50 ml PFS
  – Reserve PFS for crash carts

• Drew up batches of 50 mL syringes from large volume bags of D50

• Changed storage and stability
  – Refrigerator for 14 days

Same Drug Different Concentration

Atropine

• Usually available as a single dose prefilled syringe
  • 1 mg/10 ml (0.1 mg/ml)

• Multidose vials available
  • 8 mg/20 ml (0.4 mg/ml)

• 1 mg/1 ml vials available

Different medication

• Severe shortage of furosemide injection

• Therapeutic alternative: bumetanide

• Expedited approval from the P&T committee

<table>
<thead>
<tr>
<th>Furosemide Dose</th>
<th>Bumetanide Equivalent Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>0.25 mg = 1 ml</td>
</tr>
<tr>
<td>20 mg</td>
<td>0.5 mg = 2 ml</td>
</tr>
<tr>
<td>40 mg</td>
<td>1 mg = 4 ml</td>
</tr>
<tr>
<td>60 mg</td>
<td>1.5 mg = 6 ml</td>
</tr>
<tr>
<td>80 mg</td>
<td>2 mg = 8 ml</td>
</tr>
</tbody>
</table>

*For converting to 0.5 mg/mL bumetanide to furosemide.
**IV bumetanide is supplied as 0.25 mg/mL solution for injection. No dilution is necessary.
Different medication

Critical Shortage of Fentanyl Injection
- There is a CRITICAL national shortage of fentanyl injection.
- Morphine injection is also in limited supply as a result.
- The shortage affects IV bolus doses. Fentanyl 
  adhesions can still be used in appropriate patients.
- Hydromorphone is the preferred alternative for IV treatment of
  pain. Conversion factor is 1:15 to 20 (fentanyl:hydromorphone).
  - Fentanyl 50 mcg IV qhr = hydromorphone 0.75 to 1 mg qhr.
  - Fentanyl 100 mcg IV qhr = hydromorphone 1.5 to 2 mg qhr.
- Hydromorphone should NOT be used in patients with a
  morphine allergy (e.g., anaphylaxis).
- Alternatives for procedural sedation analgesia when rapid onset is
  needed (<3 minutes) include:
  - Ketamine (Ketalar®)
  - Meperidine (Demerol®) [plus atropine (Coral®)]

Different Medication
- Shortage of Calcium Chloride
- Reserve supply for crash cart and CT surgery
- All other areas will use calcium gluconate
- 1 gram CaCl = 3 gm Calcium gluconate

Restricting use
- Educate why limiting use and alternatives
- Expect push-back
- Consider repercussions
  - Sodium bicarbonate
  - Calcium chloride
  - Magnesium
  - Acetylcysteine

Action plan
- Monitoring
- Supply alternatives
- Therapeutic alternatives
- Restrictions
- Impact on patient care

Action plan

- Monitoring/Reallocation of supply
  - Determine critical levels
    - Estimate timeline
  - Centralize supply

- Supply alternative
  - Repackaging
  - Change product size or concentration
  - Safety considerations

Implement

- Inventory system changes
  - Purchasing
  - Storage

- Processes and procedures
  - Distribution system
  - Administration

- IT changes
  - CPOE
  - Behind the scenes
  - Order sets

- Technology changes
  - Dispensing cabinets
  - Carousels
  - Bar coding

Communicate

- Decision-makers meet routinely
  - When changes must occur
    - Include all stakeholders
      - Pharmacy staff
        - Pharmacists, technicians, buyers, informatics
      - Prescribers
      - Nursing
    - Shortage details
  - Action plan

Communication Means

- Use most effective means available
  - Many need to know
- Computerized alerts
- Paper announcements
  - Signage
  - Newsletters, medication bulletins
- Word of mouth

Notifying prescribers: CPOE alerts

Notifying prescribers: Infonet & flyers
Resolution

- Major area for improvement
- Difficult to decide when shortage is “over”
- Keeping track of changes
  - Distribution
  - CPOE alerts
  - Flyers
- Reverting to pre-shortage procedures

Conclusion

- Many reasons for shortages
- Use your resources
- Be prepared
  - Avoid crisis mode by having a plan
  - Anticipate need, error potential, and impact
  - Know everyone’s role
- Communication is key
- Patient safety is at stake
References


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