Drug Shortages and Their Impact on Anesthesiologists

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Disclosure
• I have no financial relationships with any corporate entities related to this presentation

History of Anesthesia Drug Shortages
• 1999 FDA Drug Shortage Program began
• 2000 Shortages of fentanyl, succinylcholine, and naloxone
• April 2001 meeting of stakeholders including ASA, FDA, AHA, ASHP
• Fall 2009 Increasing reports from ASA members noting shortages of propofol and succinylcholine
Drug Shortages Are Not New
ASA Newsletter: May 2004

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About 75% involved sterile injectable drugs
GAO Analysis of Univ of Utah Data

Table 4: Summary of 260 Critical Drug Shortages Reported January 1, 2009, through June 20, 2011, by Therapeutic Class

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Number of shortages</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetic and central nervous system drugs</td>
<td>61</td>
<td>23</td>
</tr>
<tr>
<td>Anti-infective drugs</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>Nurtive agents</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Oncology drugs</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Endocrine and metabolic drugs</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Toxicology antidote drugs</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Dermatological drugs</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal drugs</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Multiple therapeutic classes</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>260</td>
<td>99</td>
</tr>
</tbody>
</table>

Source: GAO analysis of University of Utah Drug Information Service and FDA data

ASA Drug Shortage Web Page

FDA Drug Shortage Web Page
History of Anesthesia Drug Shortages

- ASA began receiving multiple reports of propofol shortages from members in Fall 2009
- ASA worked closely with FDA regarding propofol shortages
  - Encouraged FDA to authorize importation of the European version of propofol (Spring 2010) which reduced shortages

Anesthesia Drug Shortages

- Shortages of multiple other drugs continued - Random impact across U.S.
- ASA working with ASHP convened Drug Shortage Summit with stakeholders and FDA
  - November 5, 2010
  - Purpose – identify various causes of shortages and any potential solutions
  - Working with partners to identify achievable next steps
Anesthesia Drug Shortages

Related ASA activity
• Advocacy for legislation
• Responded to GAO request for information
• Met with FDA representatives
• Met with HHS Secretary Sebelius

FDA Workshop – September 2011

ASA Drug Shortage Member Surveys
April 2011 and March 2012
• 3063 anesthesiologist responses (most were from U.S.)
• 98% were currently experiencing a drug shortage
• Drugs with highest frequency of current shortage
  - fentanyl 66%
  - succinylcholine 21%
  - propofol 19%
  - pancuronium 15%

Survey – Impact of Drug Shortages on Their Patients
• 67% felt patients experienced a less optimal outcome (PONV)
• 53% reported longer O.R. or recovery times
• 28% of patients complained
• 0.2% resulted in death of a patient (6)
Impact of Drug Shortages on Patients

- Although anesthesiologists are trained to safely use multiple drugs and can often find alternatives for drugs in short supply, there are implications of these shortages:
  - Decreased patient satisfaction (prolonged awakening, delayed discharge, nausea)
  - Adverse outcomes including death in extreme situations (e.g., trauma patients, unstable hemodynamics, airway emergencies)

Survey—Impact of Drug Shortages on Anesthesiologists’ Practice

- 96% had to use alternative drugs
- 50% had to change the procedure in some way
- 7% had to postpone cases
- 4% had to cancel cases

Impact of Drug Shortages on Patient Safety

- Concern regarding infection risk with splitting large vials of propofol
- Chemotherapy drugs with more side effects used when preferred drug not available
- Medication errors—Incorrect dosages when unfamiliar drugs used (HYDROMorphone given IV at doses intended for morphine; epinephrine 1:1000 vs 1:10,000)
### Types of Medication Errors

- Prescribing error
- Improper dose/quantity
- Omission error
- Wrong administration timing
- Wrong medication
- Wrong drug preparation
- Wrong dosage form
- Expired product

### Impact of Drug Shortages on Healthcare Costs

- Significantly increased prices when drugs in short supply are purchased through an alternative source ("gray" markets)
- ASHP survey estimated that national labor costs of pharmacists to deal with shortages was $216 million
- Longer procedure and recovery times drive up healthcare costs
- Societal and health system costs for cancelled or postponed cases

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**Anesth Analg 2011;113:1429-35 (December)**
Drug shortage identified

Operational assessment
1. Validate details of shortage
2. Determine stock on hand
3. Determine supply from predetermined alternative sources
4. Determine purchase history and/or true-use history
5. Estimate time to impact on the health system
6. Determine supply of alternative drug products
    (Typically done by the pharmacy department)

Therapeutic assessment
1. Identify primary patient population affected
2. Identify therapeutic alternatives
    (May be done by pharmacists or a multidisciplinary team)

Shortage impact analysis
Estimate impact on patient care
1. Therapeutic effectiveness
2. Prescribing processes
3. Distribution processes
4. Administration processes
5. Financial ramifications
    (May be done by pharmacists or a multidisciplinary team)

Establish final plan

Communicate
1. Shortage
2. Effective dates
3. Identified therapeutic alternative
4. Temporary guidelines
5. Temporary procedures

Implement
1. Information system changes
2. Technological changes (e.g., bar coding)
3. Inventory system changes
4. New procedures

U.S. Food and Drug Administration (FDA)
- Responsible for the quality, safety, and effectiveness of medications
- FDA Drug Shortage Program began in 1999
- 4 full time staff and Coordinator at time shortages began
  - Facilitate prevention and resolution of shortages by collaboration with FDA experts, industry, and external stakeholders
  - Provide shortage information to public
FDA’s Role

- Limited authority directly related to drug shortages
- Cannot dictate production quantity and must rely on voluntary participation of industry
- Pricing, transportation, and supply chain issues are not within the purview of FDA

“Just in time” production schedules

Manufacturers and distributors -- 30 day supply
Pharmacies -- 15 day supply

Information from FDA on Causes of Shortages

- Product quality/manufacturing issues (impurities, contamination)
- Delays/capacity issues
- Raw material issues
- Discontinuations (business decision)
- Increase in demand (due to another shortage)
- Loss of manufacturing site
- Component problems/shortages
- Unknown/other

Primary Reason for Disruption in Production and Supply 2010-1
Older Sterile Injectables (Generics)
- Not enough manufacturing capacity
- Industry consolidation
  -- 7 manufacturers make most of these drugs
  -- contract manufacturers
- Lack of redundancy: multiple products made on same manufacturing line
- Complex manufacturing process
- Generally not economically attractive

Drug Shortage Summit
- November 5, 2010
- Co-conveners:
  -- American Hospital Association
  -- American Society of Anesthesiologists
  -- American Society of Clinical Oncologists
  -- American Society of Health-System Pharmacists
  -- Institute for Safe Medication Practices
- Goals: Discuss scope, causes and actions needed to address drug shortages
- Meetings: April, May, June, August 2011
- Frequent discussions between ASA and FDA

FDA Public Workshop
- Held September 2011
- Presentations from oncologists, pharmacists, public
- Invited ASA presentation on impact of drug shortage on anesthesiologists
- Presentation of ASA led workgroup’s recommendations
Issue 1

- Insufficient regulatory resources to manage rapidly escalating drug shortages

- Proposed solutions:
  1. Reallocate FDA resources to Drug Shortage Program and other activities that facilitate resolution of shortages
  2. Authorize and appropriate funding for FDA activities that prevent or mitigate drug shortages

Issue 2

- Inadequate and incomplete communication of drug shortage information

- Proposed solutions:
  1. Require manufacturers to report product discontinuations and interruptions six months in advance or upon determining production will not meet average historic demand
  2. Establish communications methods to provide accurate and timely information on drug shortages to providers
  3. Establish methods to better predict the seriousness and duration of drug shortages

Issue 3

- Lack of contingency plans for critical drugs that are vulnerable to shortages

- Proposed solutions:
  1. Establish criteria for determining whether a drug is vulnerable to shortage and designate such drugs as part of the FDA approval process
  2. Establish appropriate incentives for manufacturing redundancies or other means of producing emergency supplies for drugs deemed vulnerable to shortages. The pharmaceutical industry should collaborate with regulatory and legislative entities to identify these incentives
Issue 4

• Inability to quickly respond to shortages of controlled substances

• Proposed solution:
  1. Require collaboration between the FDA Center for Drug Evaluation and Research divisions and the Attorney General to establish a process to expedite the increase in manufacturing production quotas when needed in response to shortages of controlled substances

Issue 5

• Disincentives to manufacturing older generic injectables

• Proposed solution:
  1. Leverage current FDA pathways to expedite the approval process for medically necessary unapproved drugs vulnerable to shortages without compromising quality and safety of the drug

FDA Can Help Prevent Shortages

In 2010, FDA prevented 38 shortages, and in 2011, 195 prevented by early notification

• Encourage other firms to ramp up production
• Find another manufacturer to begin production
• Expedite some regulatory processes
  --new manufacturers; production lines
  --increase expiration dates when data permits
  --new raw material sources
• Regulatory discretion for warnings or remedies (filters)
• Importation of similar products approved abroad (propofol)
FDA Action Taken for Reported Shortage

- Broader reporting by manufacturers to FDA
- Expedited regulatory review: new drug suppliers, manufacturing sites, manufacturing changes
- Report to DOJ regarding shortages that have led to stockpiling or sales at exorbitant prices ("gray market")

Presidential Executive Order
October 31, 2011

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FDA Issues Interim Rule
October 2011

Tightens restrictions on the reporting of drug shortages by manufacturers
- The sole manufacturers of critical drugs must report all disruptions in production, temporary or permanent, by providing a 6 month warning to the FDA
Risk for Shortages
Increased Reporting to FDA
• Interruptions or other adjustments in manufacturing that may adversely affect market supply
• Delays in acquiring critical raw materials or components
• Production problems that occur during or after manufacturing that could result in supply disruptions
• Import delays
• Unexpected increases in demand
Resulted in a 6-fold increase in monthly voluntary notifications

Other FDA Actions
• Significantly increased the number of staff working on drug shortages
• Development of a database to track drug shortages, causes, and fixes
• Communicated with DOJ on stockpiling
• Meeting with stakeholders including drug wholesalers to discuss development of strategies to prevent and reduce shortages

Federal Legislation: S. 3187
FDA Safety and Innovation Act
• Reauthorizes FDA’s prescription drug user fee program; allows FDA to collect fees from drug manufacturers to support FDA’s operations
• ASA and stakeholders succeeded in the inclusion of a section to help prevent and mitigate drug shortages
• Notification requirement when production of drugs used during surgery or in treatment of a debilitating disease or condition would be halted/interrupted; allows FDA to use existing authority
S. 3187
• Requires DEA to provide timely updates on decisions regarding controlled substance quota increases to help drug shortage
• Require HHS to establish a Task Force to enhance response to shortages and create strategic plan to prevent/manage shortages
• Require FDA to maintain a drug shortage list to help providers/public manage shortages
• Authorize GAO to study problem and fixes

S. 3187: Approved and Signed
• House and Senate overwhelming passed with bipartisan support
• July 9, 2012 President Obama signed the legislation

Senate Investigation of “Gray Market”
• Senate Commerce Committee; July 25, 2012
• Concerns over exorbitant prices, pedigree of drug
• Normal supply chain

  Drug manufacturer

  Primary wholesaler

  Hospital pharmacy or user
Drug Distribution and Gray Market

• Distributors have ongoing relationship with manufacturers; 85% of market by:
  AmerisourceBergen
  Cardinal Health
  McKesson
• Distributors usually place "own use" restrictions on their customers
• Some drugs in short supply are diverted into "gray markets" where they may pass through multiple middlemen, each marking up price; many do not have adequate storage facilities to ensure quality of product

Consensus Conference on the Ethics of Drug Shortages (June 2012)

• Sponsored by Emory Center on Ethics and ASA
• Topics considered
  ➢ Obligations of drug manufacturers
  ➢ Obligation to tell patients about drugs not available and use of secondary drugs
  ➢ For drugs in short supply, how should they be distributed
  ➢ Will earlier notification of shortages lead to hoarding

Reporting of Drug Shortages

• FDA at drugshortages@fda.hhs.gov
• ASHP website at http://www.ashp.org/DrugShortages/Report