Drug Shortages: Causes and Cautions

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Abstract: Drug shortages have increasingly been a problem for pharmacists and clinicians over the past decade. Clinicians need to be aware of the various causes of drug shortages and the issues that may arise as a result, particularly as they relate to medication safety. Numerous resources and strategies are available to mitigate the effects of drug shortages, and clinicians should work with their health care team and the patient to determine the best option when faced with a drug shortage that affects patient care.

Before stepping into the operating room, surgeons should be concerned with sterile garbing, proper hand-washing techniques, and the procedure they are about to perform. They are not worried whether the usual anesthetics are going to be available to put the patient to sleep. They are typically not curious if the usual vasopressor agent is available in case something goes wrong on the table. They do not have a list of backup drugs in case their agent of choice is on back order.

Unfortunately, the medical community has to start worrying about these things. Over the past 5 years, reported medication shortages have almost tripled (Figure).1 What used to be a slight inconvenience has now become a major issue in hospitals and pharmacies across the country. Many types of medications have been affected, including anesthetics, antibiotics, analgesics, and neuromuscular blockers. This article describes the typical causes of medication shortages, discusses the impact of shortages on patient care, and provides information for dealing with medication shortages.

CAUSES

The cause of the change in medication availability is multifactorial. Shortages are often due to creation, merging, and closing of manufacturing facilities and pharmaceutical companies; production issues; and a decline in the financial market. Pharmaceutical companies are often merging or being bought out by their bigger competitors, which may have ramifications on the operation of manufacturing facilities as companies consolidate resources.2 Manufacturing and production issues may also lead to shortages, particularly of sterile injectable products, which appear to be the most susceptible to manufacturing problems.3 Of the 193 drugs on shortage as of August 12, 2011, one hundred forty-nine (77%) were injectable formulations.4 The production process for injectable agents is often complex since everything must be kept sterile. To help reduce the cost of

Figure: Number of reported drug shortages by year (adapted from Larkin1).
manufacturing, multiple agents may be manufactured in the same factory, with the same equipment, or even on the same production line. This makes the company vulnerable if a line were to become contaminated or if a piece of equipment stops working. If there is failure in the process, multiple drugs can be affected. Alternatively, if impurities are found in a sterile vial or if a drug product does not contain the proper amount of active ingredient, the entire lot (or batch) of drug will be recalled. Some examples of injectable drugs recently on short supply or back order include propofol, lorazepam, labetalol, and haloperidol lactate.

Another more recent contributing factor to the rise in drug shortages is economics. Companies may choose to stop making a product entirely, either because generic competition is financially burdensome, the process is too costly to maintain and make a profit on the drug, or there is declining use due to newer alternatives. Also, companies may decide to put their efforts into manufacturing a newer, more profitable on-patient medication. Another unappreciated effect of the recession is that less reserve inventory of medications is typically maintained by pharmaceutical companies. Rather than have a warehouse full of medication ready to ship, companies may elect to make less product, merely meeting the needs of consumers rather than ensuring a slight excess. This saves money by decreasing the inventory on the shelf, but if the manufacturing process is compromised in any way, there is no reserve stock for the company to draw from, thereby creating a shortage.

CAUTIONS

Numerous problems have been documented due to medication shortages. In some instances, there are no viable alternative therapies, and clinicians are forced to do nothing, rather than use an alternative agent. One example of this rare scenario was during the methylprednisolone shortage, which likely resulted in a number of patients with acute spinal cord injury not being able to receive high-dose methylprednisolone therapy immediately after their injury, potentially limiting the extent of neurologic recovery. More often, other agents are available that can replace the agent on back order, although in many instances the agent may be less preferable or more associated with adverse effects. Alternative agents are often less familiar to clinicians, so dosing and administration errors may be more common.

Some medication shortages have dramatically affected patient care. For example, 1 patient succumbed to a multidrug-resistant Pseudomonas infection (only susceptible to amikacin, which was unavailable at the time) due to inadequate therapy. Another patient with resistant organisms had to be re-admitted to the hospital after failure on inadequate alternative drugs. The substitution of 1 drug for another allows another opportunity for error. A neuromuscular blocker shortage (vecuronium) was associated with some patients receiving the wrong neuromuscular blocker dose due to mistakes in drug selection. Two patients experienced pulmonary hypertension related to receiving rocuronium when the preferred agent was not on hand. Due to a calculation error in converting 1 narcotic to another, 2 patients died when intravenous hydromorphone was substituted for intravenous morphine at the same dose.

More frequently, clinicians are forced to select from agents that are comparable in efficacy but have subtle differences in half-life, drug–drug interactions, or adverse effects. In some instances, the substituted medication may be less studied for this particular use or less appropriate for the clinical situation, or may have a higher risk of adverse drug reactions than the original product. A good example of this situation is the propofol shortage. Since autumn 2009, the anesthetic drug propofol has been facing production issues. For institutions lacking propofol, other options for sedation include midazolam or dexmedetomidine. Both agents are similar to propofol but do not precisely mirror the quick time to onset and offset or level of sedation provided by propofol. Midazolam has a longer duration of action (1-4 hours vs 6-20 minutes for propofol). Dexmedetomidine is similarly short acting compared to propofol, but is more costly and more associated with hypotension and bradycardia. One substitution to dexmedetomidine led to a medication error when it was given at an improper rate. The patient received 20 times the appropriate dose for 5 hours, likely due to unfamiliarity with what was a new drug at the time. Another patient was changed to midazolam, which was incorrectly given at the rate appropriate for propofol. The patient became overly sedated.

An issue that is not directly related to individual patient care but that may have effects in the future is the increased cost related to drug shortages. Costs are increased on multiple levels. Patients have a higher copay for brand name vs generic drugs. Insurance companies may have to pay more for higher-cost drugs. The hospital’s or practice’s revenue from a procedure may decrease if they are forced to use a more expensive drug but still receive the same reimbursement. They may also lose money if operative procedures are scheduled and then not performed due to a unique drug product being on short supply. One recent example that impacted budgets was the shortage of unfractionated heparin syringes (due to adulterated product). Many institutions were not able to use heparin for prevention of venous thromboembolism (VTE), resulting in an increased use of low-molecular-weight heparins (equally or more effective agents for most patients requiring VTE prophylaxis, but also more costly). Similarly, the recent shortage of vecuronium resulted in the increased use of rocuronium. These agents are largely unfamiliar to nonanesthesiologists, but have moderate differences in their duration and large differences in their dosing, making a lack of familiarity with these agents a potential problem.
Another area in which drug shortages might have long-lasting effects is clinical research. Cancer research appears to be the area most affected thus far. Many of the unavailable drugs are cancer treatment drugs or medications used to treat or avoid the side effects of chemotherapy regimens. If a certain drug protocol is required for the clinical trial but the drug becomes unavailable partway through the trial, researchers are forced to change their medication plan. This could compromise the design and conduct of ongoing trials, which can lead to difficulties in data analysis and interpretation.1

**STRATEGIES**

When a clinician is faced with a drug shortage, some strategies may be used to address the situation. First, the drug that is unavailable can be switched to a different formulation of the same drug. For instance, if a generic manufacturer has a shortage of medication, the brand name drug may be used instead of the generic. Similarly, different formulations may be used instead (such as in the case of the intravenous dexamethasone shortage, where many patients were converted to oral or enteral administration). If all formulations of the medication are unavailable, a different but similar product can be substituted. Clinicians should consider the different dosing regimens, adverse effects, and pharmacokinetics (duration of action, half-life) of the alternative agents.

When choosing an alternative antibiotic in the setting of a shortage, there are a few things to consider. First, the same microbiologic spectrum of activity is necessary. In the case of a penicillin shortage, alternative agents for *Clostridium* infection after an open fracture might include clindamycin, metronidazole, or a carbapenem. Consideration of the compartment with potential infection is also important. If there is a possibility of osteomyelitis, sufficient bone concentrations are necessary. Drug metabolism and elimination also need to be taken into consideration, particularly in patients with renal or hepatic insufficiency. Commonly used antimicrobials such as clindamycin, metronidazole, amikacin, rifampin, vancomycin, bacitracin, doxycycline, acyclovir, cefotetan, tobramycin, and fluconazole may have been unavailable in certain hospitals recently, causing practitioners to deal with many of these drug selection issues.4

To be most prepared for unavoidable drug shortages, health care providers should be aware of the institution’s plan of action. This plan should include how prescribers are notified of upcoming or possible drug delays.1 In many instances, the pharmacy will first be aware of any drug supply issues. When there is a question regarding drug substitution, a pharmacist is a logical choice to call for help. They have the knowledge and information resources to answer drug-related questions. In addition, guidelines for various therapeutic issues typically discuss the alternatives for therapy and the literature pertinent to the selection of 1 agent over another.

If one’s institution does not have a definite plan for dealing with unavailable drugs, the prescriber may have to do their own research. Again, a phone call to the pharmacy may be helpful. There are also 2 good resources available online. The American Society of Health-System Pharmacists (ASHP) Web site keeps the most current list of drugs that are currently on shortage or that may become unavailable in the near future.4 The listed drugs can be searched by date or in alphabetical order. The site may list information as to why a drug is having production issues and which particular manufacturers are affected, and may even suggest substitutable drugs. The Food and Drug Administration also has a Web site devoted to drug shortages, but their list is not as comprehensive as that of ASHP.

As drug shortages become a daily occurrence in hospitals and pharmacies across the country, prescribers need to be aware of the problem and should be prepared to act when faced with an unavailable drug product. Institutions should have a protocol to deal with drug shortages, and all prescribing health care providers should be familiar with it. If not dealt with properly, a back-ordered medication can affect patient care and possibly lead to worsened patient outcomes.

**THE BOTTOM LINE**

- Drug shortages are increasing in occurrence and are having impact on patient care.
- Substitutions for unavailable products must be carefully selected, with physicians considering differences in indications, pharmacokinetics, and side-effect profiles.
- Clinicians should be familiar with their individual institution’s plan for handling drug shortages.

**REFERENCES**