REVIEW ARTICLE

US Propofol Drug Shortages: A Review of the Problem and Stakeholder Analysis

Christopher Hvisdas, PharmD Candidate; Andrea Lordan, PharmD Candidate; Laura T. Pizzi, PharmD, MPH; Brandi N. Thoma, PharmD

Background: Drug shortages have increased in recent years in the United States, with a majority involving sterile injectable drugs. Propofol, a sterile injectable drug, is frequently used as a sedative, thanks to its rapid onset of action and a short recovery period. However, propofol is complicated and expensive to manufacture, and recent events involving major manufacturers have led to shortages of the drug in the United States.

Objectives: To review the events leading to the shortage of propofol and to discuss how the shortage is affecting various healthcare stakeholders, as an example of the systemwide problem of drug shortages in the United States.

Discussion: Manufacturers currently have little economic incentive to produce propofol, a generic drug whose production is costly and carries a high liability. The enforcement of good manufacturing practices by the US Food and Drug Administration is beneficial for the safety of US citizens, but it can inherently lead to a sudden halt in the manufacturers' production of drugs. Hospitals are affected because they must develop a plan to address current and potential shortages, including restricting the use of medications that have a shortage and shifting to alternative agents.

Conclusion: The shortage of propofol significantly impacted the delivery of care in the United States in 2009, and various stakeholders are working to increase the existing supply of propofol and to investigate the use of alternative medications when the supply runs short. The case of propofol presented in this article is used to illustrate a systemwide view of the impact of drug shortages on the US healthcare system.

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In recent years, drug shortages have become a common occurrence in hospital and retail settings, with a record high of 267 drug shortages reported in 2011.[1] Julie A. Golembiewski, PharmD, Clinical Associate Professor, Departments of Pharmacy Practice and Anesthesiology, University of Illinois at Chicago, defines a drug shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA [US Food and Drug Administration]-regulated drug is inadequate to meet the current or projected demand at the user level."[1] The impact and prevalence of such drug shortages were illustrated by a 2011 American Hospital Association survey of community hospitals.[2] Nearly 50% of the responding hospitals reported ≥21 drug shortages within the first 6 months of 2011, and more than 99% of hospitals reported at least 1 drug shortage.[2]

Mr Hvisdas and Ms Lordan are Doctor of Pharmacy students and Dr Pizzi is Associate Professor, Department of Pharmacy Practice, Jefferson School of Pharmacy, Philadelphia, PA; Dr Thoma is Clinical Pharmacy Specialist, Surgical Cardiac Care Unit, Thomas Jefferson University Hospital, Philadelphia, PA.

Approximately 80% of drug shortages involve sterile injectable drugs, such as anesthesia agents and chemotherapy drugs.[1] These drugs can be difficult and expensive to manufacture, thereby forcing companies to operate on slim profit margins and leading to other companies exiting the market altogether.[3] Currently, 3 pharmaceutical companies account for 70% of the sterile injectable products manufactured in the United States.[1] The FDA maintains a useful website on drugs (www.fda.gov/Drugs/DrugSafety/DrugShortages) that provides notifications regarding drug shortages, guidelines on shortage management, and the agency's actions to address specific shortages.

Propofol, one of the sterile injectable drugs that is currently experiencing a shortage, is a phenolic derivative with sedative and hypnotic properties that is frequently used in intensive care units.[4] It is formulated as an oil-in-water emulsion for intravenous use, which makes it highly lipophilic and allows it to rapidly cross the blood–brain barrier.[4] Propofol is also quickly redistributed into peripheral tissues and is metabolized, resulting in a rapid onset of action, as well as a rapid emergence from sedation, making it the preferred choice for many anesthetists.[4]

KEY POINTS

- Drug shortages are common in hospitals and retail settings across the United States with serious impact to all healthcare stakeholders.
- The majority of drug shortages involve sterile injectable agents.
- Propofol is often used as a sedative and is undersupplied for the demand in the United States; manufacturers of this drug need greater financial incentives to produce it.
- The FDA can help to resolve drug shortages by enforcing good manufacturing practices and by designating alternate suppliers.
- Hospitals must develop plans to address shortages, including restrictions on drug use and using alternate agents.
- The propofol shortage had implications for various stakeholders, including patients, providers, payers, and drug manufacturers. This case is a good example of the impact of drug shortages overall on the US healthcare delivery system as a whole.

Two major problems led to a recent shortage of propofol in 2010. After an outbreak of hepatitis C resulting from the inappropriate, unsanitary use of propofol, a verdict was issued against Teva Pharmaceuticals, which held 40% of the US market share at the time.[3] As part of this ruling, Teva was ordered to pay $356 million to 1 man who developed hepatitis C, and their partner, Baxter International, was ordered to pay $144 million.[3] The precedent set by this ruling discourages companies from making drugs with a high liability risk, especially when the court system unfairly holds pharmaceutical manufacturers responsible for the misuse of their products.[3] It should be noted that the manufacturers' marketing of oversized vials may have contributed to a hepatitis C outbreak, because the practice of reusing such vials inherently poses a risk of infectious contamination.

The second major problem deals with noncompliance with the FDA's good manufacturing practices. In 2010, Hospira, Inc, voluntarily closed its manufacturing plant in North Carolina to address quality assurance and regulatory issues that had been identified during inspections by the FDA.[1] This plant has remained closed for most of the past 2 years, focusing its efforts on becoming FDA compliant.[1]

An additional factor that has affected propofol availability was a voluntary recall of select lots of propofol that were manufactured by Hospira.[5] The recall was issued as a result of possible contamination with particulate matter on March 31, 2010, and was extended nationwide on May 27, 2010, resulting in a shortage of propofol between April 1, 2010, and June 30, 2010.[5] As manufacturers continue to merge, fewer companies provide a larger portion of a drug's supply. Problems with one of these companies, such as the recall by Hospira, can lead to a sudden shortage of a drug.

In critical care, drugs are chosen for a certain condition based on their efficacy, pharmacodynamics, pharmacokinetics, bioavailability, or actions on distinct receptors.[6] However, in recent years, with the epidemic of drug shortages, medications are sometimes chosen simply because they are the only ones available.[6] Drug shortages, including that of propofol, can alter how the pharmacy dispenses or prepares medications, as well as affect government regulation of pharmaceutical manufacturers and patient care, especially when alternative medications must be used in place of the preferred drug.

Stakeholder Analysis

Government

The government, the FDA in particular, has a responsibility to resolve issues that adversely affect the safety and well-being of US citizens. Drug shortages, which can affect the treatment of life-threatening diseases, are an important issue that the FDA needs to address. One contributing factor to the propofol shortage was the FDA's increased enforcement of compliance.[7] Drug manufacturers now only have 15 days to respond to issues found in good manufacturing practices during inspection before the FDA issues a warning or takes corrective action.[7] Of the 5 major generic companies producing injectable drugs, 4 underwent remediation simultaneously to comply with this new policy, causing a sudden halt in the production of many drugs.[7]

Manufacturers are now required to notify the FDA if a drug has the potential to be in short supply, along with reasons and expected unavailability, whereas the previous law only required this in cases where there was only 1 manufacturer of a given drug.[8] On receipt of notice of potential shortages, the FDA then works to resolve any underlying causes, such as manufacturing or quality issues.[8] In the meantime, the FDA reaches out to other suppliers of the drug to help increase the overall production of the product and expedites processes needed to increase production, such as the approval of new production lines.[8] In cases where US drug companies are unable to resolve manufacturing issues in a timely manner, such as with propofol, the FDA searches abroad for companies that are willing and able to import similar products of adequate quality that pose little to no risk to US patients.[8]

Currently, according to the American Society of Anesthesiologists, propofol should be treated as "deep sedation," and therefore should only be administered by people who are trained in general anesthesia administration and who are not directly involved in the medical procedure being done.[9] Because of this, propofol is usually administered by an anesthesiologist or a certified nurse anesthetist in a process called monitored anesthesia care (MAC). This procedure is not very cost-effective, especially in healthy persons who are undergoing routine procedures. Adding MAC to a procedure creates an additional fee; the Centers for Medicare & Medicaid Services pays an average of $155 for the addition of MAC to an endoscopy, whereas private insurers pay an average of $437 for the same procedure.[9] However, alternatives to propofol may be even more costly.

Dexmedetomidine, one of the major proposed alternatives to propofol, is currently much more expensive than propofol or midazolam (another proposed alternative). Dexmedetomidine has a median per-patient drug acquisition cost of $1166 compared with only $60 for midazolam.[10] Because dexmedetomidine will lose its patent in 2013, its acquisition price is expected to decrease dramatically, which may make it a viable alternative in the future.[10]

Pharmaceutical Suppliers: Manufacturers and Purchasing Organizations

The current propofol shortage is a result of the supply being unable to meet the demand. As the source for all drugs, drug manufacturers are directly responsible for the supply of propofol in the market. In 2009, only 3 drug manufacturing companies were producing propofol for the US market.[11] One of these companies, Hospira, temporarily stopped producing propofol, whereas Teva decided to stop its production of this agent completely.[11] It was clearly impossible for the remaining manufacturer, APP Pharmaceuticals, to produce enough propofol to meet the demand of the entire US market.[11] Although there is a great demand for this drug, most manufacturers are unwilling or are unable to produce propofol, which has been a major roadblock to alleviating the shortage.

One of the major reasons for the limited production of propofol is that there is very little economic incentive for manufacturers to produce the drug. Propofol, a sterile injectable drug, is both complex and time-consuming to produce. Some manufacturing companies simply do not have the capacity to produce such a drug, whereas many companies that do have the capacity are unwilling to invest the extra money and time that are necessary to manufacture it.[11] Furthermore, because propofol is a generic drug, it commands a much lower price in the market than a patent drug, and any profits that could be earned from its production are minor. In addition, the ruling against Teva in 2010 has made manufacturing companies more wary of producing drugs with high liability.[3] Therefore, from the perspective of the manufacturers, the benefits of supplying propofol are outweighed by the costs and the risks, and it is much more logical to produce drugs that are easier to manufacture and that can be sold for a higher price.[11]

Group purchasing organizations also contribute to the issue. Group purchasing organizations generally select a preferred manufacturer, which guarantees demand for a particular product for that manufacturer.[7] Because of this, there is constant competition between drug companies to make a product in large quantities to win group purchasing organization contracts, which drives product prices down and ultimately lowers profit margins.[7] If a company is unable to win a group purchasing organization contract for a drug, it has much less financial incentive to continue producing the drug.[7] In addition, this "exclusivity" decreases incentive for other companies to enter the market, which keeps the market small.[7] If there is an issue with production at a preferred manufacturing company, there are little to no other suppliers of the drug, thus causing a shortage when demand cannot be met.[7]

Although high demand for a drug on shortage can increase its price and can create an incentive for more manufacturers to enter the market, this is only a temporary situation. As soon as more supply enters the market, the price will drop, creating a disincentive for new drug manufacturers to enter the market. Because manufacturing companies are not increasing the supply to fill the gap left by the recall of large amounts of propofol or the withdrawal of major propofol manufacturers from the market, the shortage with propofol persists.

Hospitals

Hospital administrators typically step in to regulate the dispensation of medications during drug shortages. This requires significant effort on the part of hospital administrators, who must analyze and determine how best to address the shortage based on the volume and the types of medical procedures. Ultimately, however, all hospital employees are affected by a drug shortage: they need to be apprised as to which drugs are approved for procedures, ensure that appropriate alternatives are available, and they must quantify all medications on shortage to regulate their distribution. Given the number of recent drug shortages, this is no simple task.[1]

A major challenge for hospitals is to quickly develop a clear plan for addressing the shortage and to ensure that this plan is communicated to its clinicians, its staff, and when necessary, to its patients. A study conducted in 2012 presented specific drug shortage management approaches to be used by hospitals, advocating a reliable process that developed a hierarchy of clinical need.[12] The study promoted the distribution of medications on shortage to patients who needed them the most.[12]

Hospital administrations can develop such a hierarchy through their Pharmacy & Therapeutics (P&T) committees. For example, in response to the recent propofol shortage, in October 2012 our hospital's P&T committee limited the use of propofol to traumatic brain injury, bedside invasive intracranial procedures, spinal cord injuries, nontraumatic subarachnoid hemorrhage, ventilated acute liver failure, refractory status epilepticus, and ventilated stroke. In addition, the availability of propofol within Pyxis units was restricted to a select number of intensive care units.

Restricting the use of a drug on shortage to patients and procedures that rely on it most heavily is a sensible and ethical solution; however, it is not a long-term solution, and it only provides temporary relief. Also, limiting the use of medications that are on shortage can lead to an important drug being unavailable during an emergency, a situation that is both frustrating for hospital staff and potentially dangerous for patients.

In rare cases, a restricted drug may lead to improved outcomes as a result of using an alternative agent. After the propofol shortage at our institution, cardiac surgery intensivists began using dexmedetomidine for sedation immediately postoperatively. In a comparative analysis, more patients sedated with dexmedetomidine were extubated within a goal of 6 hours compared with patients sedated with propofol ($P = .001$). This contributed to a significant decrease in overall length of stay in the patients receiving dexmedetomidine ($P = .012$).[13]

The Search for Cost-Effective Alternatives

Propofol is favored as a sedative because it is potent and has a rapid onset of action with a relatively short recovery period.[4] As a result, it is the sedative of choice amongst physicians for many procedures. In practice, certain medications—dexmedetomidine and midazolam—may effectively replace propofol in certain clinical settings. A 2012 study conducted by Jakob and colleagues analyzed the differences between dexmedetomidine, midazolam, and propofol in prolonged mechanical ventilation.[14] The results demonstrated that dexmedetomidine was as effective at sedating patients who are on mechanical ventilation in an intensive care unit setting as midazolam and propofol.[14] In this particular study, patients given dexmedetomidine were better able to communicate their pain levels and were more easily aroused compared with patients sedated with propofol or with midazolam.[14] This is an important advantage, because it allows clinicians to communicate with sedated patients, which permits the clinicians to better perform procedures. However, more adverse events were observed with dexmedetomidine, and it had a longer onset of action than that of propofol.[14]

From an economic standpoint, there is a significant difference in price-per-patient drug costs between dexmedetomidine and propofol. One study showed that patients who were sedated with dexmedetomidine during coronary artery bypass graft (CABG) surgery or with valvular surgery had $50 more in sedation-related costs per patient.[15] However, emerging evidence suggests that these additional sedation costs can be offset by reduced intubation time and by reduced intensive care unit length of stay with dexmedetomidine. At our hospital, we examined data for patients undergoing CABG surgery and reported an estimated $4246 cost-savings per case for the use of dexmedetomidine versus propofol.[13] This estimate reflects the positive financial impact that the transition to dexmedetomidine can have on patient and hospital expenses.

Conclusion

Overall, the propofol drug shortage has impacted various stakeholders with differing perspectives in ways that immediately affect the US healthcare system. Drug manufacturers need financial incentives to undertake the risks that are associated with the production of propofol, and they should promote single-use packaging to reduce the likelihood of contamination. Hospitals are stressed by their efforts to distribute their remaining propofol and to acquire more propofol from the limited supply. Physicians are concerned with providing efficacious sedation to patients. It is evident that the propofol shortage has significantly impacted healthcare delivery and that it serves as an interesting case study to inform stakeholders' efforts to proactively identify and manage future drug shortages. This case of propofol shortage is one example of the impact of drug shortages overall on the US healthcare system as a whole and why it is urgently necessary to address such shortages. ■

Author Disclosure Statement

Mr Hvisdas, Ms Lordan, Dr Pizzi, and Dr Thoma have reported no conflicts of interest.

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STAKEHOLDER PERSPECTIVE

Drug Shortages in the United States Continue to Undermine Patient Care

By Jack E. Fincham, PhD, RPh
Professor of Pharmacy Practice and Administration, University of Missouri-Kansas City School of Pharmacy

POLICYMAKERS: Mr Hvisdas and colleagues' exceptionally well-written analysis of the incidence, impact, and outcomes of drug shortages in the United States is timely. Their discussion provides an excellent example of how the shortage of one drug, in this case propofol, can impact so many stakeholders in differing aspects of healthcare delivery in the United States.

And although as of May 31, 2013, the US Food and Drug Administration (FDA) classifies the drug shortage of propofol as "resolved: no supply issue anticipated,"[1] many other drugs have experienced drug shortages. The article by Mr Hvisdas and colleagues gives providers, governmental policymakers, manufacturers, patients, and regulatory entities a comprehensive overview of the significant, negative outcomes that occur with the understated problem of drug shortages in the United States.

To further focus attention on the importance of the topic of drug shortages in the United States, it is important to note that as of June 6, 2013, the FDA lists 130 drugs in the Current Drug Shortages Index.[2] Therefore, the suggestions outlined in this article by Mr Hvisdas and colleagues provide a sound base for future situations that may result from drug shortages.

As early as 2010, Jensen and Rappaport noted that sterile injectable drugs, such as propofol, are susceptible to problematic drug shortage issues.[3] The authors discussed the serious issues that are affecting all those involved when these types of crucial drugs are in short supply.[3] Referring specifically to drugs required for anesthesia, De Oliveira and colleagues suggest that patient safety is at risk by an increased probability for medication errors occurring more frequently as a result of the environment becoming conducive to confusion and subsequent errors from drug shortages.[4]

Rider and colleagues propose the use of an expanded-phase approach to dealing with drug shortages.[5] This approach involves several phases, including a preparation phase that is focused on multidisciplinary risk management, followed by a contingency phase that incorporates a drug shortage task force, as well as an assessment phase that examines the outcomes of the systemwide approach to analyzing drug shortages.[5]

Furthermore, drug shortages and their critical nature have had an international reach and reaction as well. In Canada, similar assessments and calls for action have been deemed crucial for the Canadian anesthesia milieus.[6,7]

PROVIDERS/PATIENTS: A more focused approach to dealing with drug shortages at the outset of any potential occurrences needs to be incorporated into academic and clinical settings—in the institutional setting and the community setting—to a much greater extent than is presently in place. Patient safety should be the driving force to making these changes a real outcome of the dangerous situation that puts patients at risk and has undermined, and continues to undermine, patient care.

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