PPM ANESTHESIA & the LAW
A RISK MANAGEMENT NEWSLETTER

DON'T SETTLE. OWN. ™ ISSUE 27

Propofol Shortage Continues to Create Patient Safety Concerns and Risks for Anesthesiologists

Causes of the Shortage

The propofol shortage began in 2009 when two manufacturers halted distribution and recalled several lots of propofol products because of quality problems. In July 2009, Teva Pharmaceuticals (Teva) recalled five lots of its propofol after 20 patients who received the drug had adverse reactions with flu-like symptoms. The company discovered high levels of endotoxin, apparently linked to contaminated egg yolk used in the manufacturing process, in vials of the sedative pulled from the affected lots. In November 2009, Teva recalled eight more lots as a precaution. In March 2010, Teva placed all of their propofol manufacturing on hold. In May 2010, Teva, previously the largest distributor of propofol in the United States, informed the FDA that it had halted all manufacturing of propofol and would not resume production or distribution of this drug.

The propofol shortage was compounded by manufacturing problems at Hospira, one of three U.S.-based propofol manufacturers. In October 2009, Hospira recalled several lots of their propofol after discovering metal particles in the lots. According to a Hospira spokesperson, no patients were harmed by the problem. Hospira has notified the FDA that it has improved its manufacturing process for propofol and has resumed production, but has not released any new propofol yet because the FDA is still reviewing its manufacturing changes. The FDA anticipates Hospira will resume full production of propofol by fall 2010.

APP Pharmaceuticals, the only other U.S.-based propofol manufacturer, has increased its production of propofol (Diprivan), but cannot keep up with the increased demand.

Further complicating the propofol shortage is the fact that some of the drugs that could be used in place of propofol are also in short supply. Supplies of Hospira's anesthetic thiopental (Pentothal), the leading alternative to propofol for many facilities, are also limited due to manufacturing issues.

FDA's Response to the Propofol Shortage

In response to the national propofol shortage, the FDA is working with U.S.-based propofol manufacturers to address these shortages. The FDA has also temporarily allowed importation of Fresenius Propoven 1% (Propoven) into the United States. Although Propoven is an unapproved drug

In this Issue

Propofol recently garnered world-wide attention when it was discovered that pop-singer icon, Michael Jackson, was being administered propofol by his personal physician as a sleep aid and likely contributed to his untimely death. Propofol was also the drug at issue in a recent record-setting, multi-million dollar verdict returned by a Las Vegas, Nevada jury against a propofol manufacturer and distributor. Propofol is once again in the news due to an ongoing national shortage of this commonly and widely used anesthetic agent. In response to the national propofol shortage, the Food & Drug Administration (FDA) has temporarily authorized the importation of an international propofol product as a clinically acceptable substitute. In this issue, we examine the causes of the recent propofol shortage and the significant patient care and safety concerns the shortage has created. We also highlight the differences and potential risks between using the U.S.-marketed propofol and the international propofol substitute. Finally, we offer some risk management advice to PPM policyholders to avoid potential liability from the use of propofol and the propofol substitute.

Thanks for reading,

Brian J. Thomas, Editor

product in the United States, it is currently approved in other countries. Under specific circumstances, the FDA has the discretion to allow the importation, distribution, and use of unapproved drugs to address severe drug shortages and public health emergencies. The FDA ensures the quality of these drugs through close inspection of the manufacturing facilities and evaluation of available safety and efficacy data. The FDA has determined that Propoven is comparable to the propofol used in the United States.

Implications for Patient Care

PPM policyholders should be aware there are significant differences between propofol and Propoven that could affect patient care and create potential liability exposure. According to APP Pharmaceuticals and the FDA[*], the differences between propofol and Propoven are:

- Propoven does not contain an antimicrobial component. **STRICT ASEPTIC TECHNIQUE SHOULD ALWAYS BE USED DURING HANDLING OF ANY PROPOFOL OR PROPOVEN PRODUCT.**
- Propoven vials are for **SINGLE-USE ADMINISTRATION ONLY. VIALS ARE NOT INTENDED FOR MULTI-DOSE USE.**
- After being drawn up into a syringe, the syringe should be discarded after six hours; any unused portion of a vial should be discarded immediately following vial penetration.
- Although the Propoven label indicates that it may be used for general anesthesia in pediatric patients down to one month of age, it is recommended that, in keeping with the U.S. propofol labels, Propoven be used for maintenance of anesthesia in patients above the age of two months. Propoven may be used for induction of anesthesia in patients above the age of three years.
- Propoven should not be used for sedation in patients less than 16 years of age.
- Propoven is contraindicated in patients with soy or peanut allergies.
- Propoven contains both medium-chain triglycerides and long-chain triglycerides, in contrast to propofol products that contain only long-chain triglycerides. PPM policyholders are cautioned to take this difference into account for patients receiving total parenteral nutrition (TPN), patients with fat metabolism disorders, or patients in which lipid emulsions must be used cautiously.
- Propoven's barcode may not be recognized in U.S. facilities employing barcode scanning systems. Alternative procedures should be followed to verify correct drug product prior to patient administration.

Rationing and Alternative Agents

Although it is possible to break 50 ml and 100 ml vials of propofol, which are intended for infusions, into smaller doses for injections, the FDA and PPM strongly discourage such practice even under sterile conditions. "No vial of propofol is meant as a multi-dose vial," according to FDA medical officer Arthur Simone, M.D.

Even with the availability of Propoven, anesthesiologists and health care facilities continue to struggle to obtain propofol and suitable alternative anesthetics. Some hospitals and health care facilities are calling on anesthesiologists to cut back on their use of the drug by switching to an alternative induction agent such as methohexital, etomidate or sevoflurane; avoiding propofol for "marginal indications" like general anesthesia, reducing post-operative nausea and for patients undergoing prolonged intubation; and substituting other drugs, such as fentanyl, midazolam, dexmedetomidine. Facilities are also admonishing anesthesiologists to be frugal with propofol by not drawing propofol up in a syringe until they are certain of use. Other hospitals and outpatient surgery centers without a propofol supply have had to transfer patients to facilities possessing the drug. In other instances, patients have had elective surgeries postponed. Some PPM policyholders have reported their facilities without a propofol supply have had to shut down operations completely until additional propofol becomes available from suppliers.

[*] Correction: This sentence in our original newsletter has been altered to clarify that the differences described are those provided by the drug's distributor, APP Pharmaceuticals, along with the FDA. Questions regarding information provided by the drug's distributor should be directed to APP Medical Information at 1-800-551-7176 between the hours of 8am and 5pm (CST) or e-mail at appmedicalinfo@APPpharma.com.

$500 Million Jury Verdict Awarded Against Propofol Manufacturer and Distributor

In May 2010, a Clark County, Nevada jury returned a $500 million punitive damage award against Teva and Baxter Healthcare Services (Baxter) on several product liability claims related to propofol. Teva, the propofol manufacturer, was ordered to pay $356 million and Baxter, the distributor, was ordered to pay $144 million. The jury verdict was the largest award in Nevada's history.

The lawsuit was brought on behalf of one of nine patients linked to two Las Vegas, Nevada endoscopy clinics where approximately 50,000 patients were exposed to hepatitis B, hepatitis C, HIV and other blood-borne diseases. Practitioners at the endoscopy clinics allegedly used 50 ml, single-use vials of propofol to obtain multiple doses, contrary to label recommendations. The plaintiff alleged he contracted hepatitis C at Desert Shadow Endoscopy Center in 2006 during a routine colonoscopy.

Plaintiffs argued that the drug packaging did not include appropriate warnings against reusing vials between patients. Plaintiffs also argued that 50 ml vials of propofol should not have been sold to endoscopy centers because they tempted nurses to reuse the vials instead of throwing away unused portions. Plaintiffs argued further that despite previous outbreaks and knowledge that 50 ml vials were being misused, the defendant companies continued to make and sell them to endoscopy centers because they were more profitable than safer 10 ml vials.

Defense lawyers for the defendant drug companies argued that the drug warning label indicated "single-patient only" and aseptic procedures should be used at all times. The defendants argued further that selling the differently sized vials gave medical professionals the choice of deciding which were appropriate for their patients and procedures.

The jury had previously awarded the plaintiff and his wife compensatory damages of $3.25 million and $1.85 million, respectively.

Plaintiffs made a $1.7 million settlement offer before trial that was rejected by the defendants. Both defendants plan to appeal the judgment.

No Nevada PPM policyholders were implicated in the hepatitis outbreak. Therefore, the impact of any resulting litigation will not be borne by PPM policyholders.

Conclusion

Drug shortages can have a profound effect on patient care since they limit the treatment options available to health care practitioners and patients. Additionally, PPM policyholders face significant potential liability exposure from the risks associated with misusing a product. PPM strongly advises it policyholders to continue to scrupulously adhere to label instructions for the use of any drug, even during a time of shortage. Although this advice is true for all drugs in general, it is especially important for sterile, injectable products such as propofol. In the case of propofol, the FDA has received numerous reports of adverse events resulting from multiple entries into single-use vials of propofol to obtain multiple doses, contrary to label recommendations. This dangerous practice has resulted in life-threatening illnesses due to contamination. And, as illustrated above, this dangerous practice has also resulted in multi-million dollar jury verdicts against health care practitioners and drug companies. PPM policyholders are also advised to determine any contraindications before administering any drugs, including patient allergies to soy, nuts or eggs.

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