Propofol Guidance

April 22, 2020

URGENT REQUIREMENTS:

- The practice of changing propofol administration sets less frequently than 6-12 hours is NOT recommended.
- The practice of pooling propofol is NOT recommended. The process of pooling propofol is to be used ONLY during times of extreme propofol shortage, after consultation with supply chain/pharmacy and system office, when ability to identify additional 50 ml or 100 ml of propofol OR adequate supplies of alternative agents is not feasible.
- Propofol is lipid based and preservative-free, increasing the risk of contamination if the above best practices are violated.

RECOMMENDATIONS:

1. The recommended frequency for changing propofol administration sets based on package inserts and Infusion Nurses Society (INS) is 6-12 hours in order to avoid bacterial and fungal growth. Extending the frequency that administration sets for propofol need to be changed IS NOT PERMITTED.
2. MercyOne does not recommend pooling propofol for administration. During this time of medication shortages, this might need to become an option, but sites must first:
   a. Consult with supply chain and system office/pharmacy to identify if additional supply of 50 ml or 100 ml sizes of propofol are available OR if adequate supplies of alternative agents are available for utilization.
   b. After consultation with system office and confirmation that other options are not available, pooling of propofol, must adhere to the following steps:
      i. Pooled propofol CANNOT be batched in advance, and MUST be assigned for immediate use
      ii. Pooled propofol should be added to either sterile empty vials or PVC-free bags (Baxter INTRIAVIA) in the pharmacy under sterile conditions
      iii. Final pooled product MUST not be hung for greater than 6 hours.
      iv. Adverse reactions must be reported immediately to pharmacy via incident reporting system

RATIONALE

In response to the increased utilization and shortage of 100 mL vials of propofol, pooling smaller vial presentations has been proposed or changing propofol tubing less frequently than recommended by the manufacturer have been recommended. Significant considerations for pooling propofol include its stability in other containers, oxidation, microbial contamination, and operational considerations. Propofol is more stable in glass, polypropylene (PP), and polyolefin containers than in polyvinyl chloride containers (PVC) due to its adsorption to PVC. When exposed to oxygen, propofol undergoes oxidative degradation.
The implications of oxidation when pooling propofol are unknown. Propofol's lipid base supports the growth of microorganisms.\textsuperscript{1-5} This requires strict aseptic procedures during handling and a limited beyond-use date (BUD), typically 6 or 12 hours.\textsuperscript{1-5,11-13} Operational considerations include the product's final volume and concentration, preparation and administration time, nursing and pharmacy communication, and final container and intravenous (IV) line characteristics.

CONSIDERATIONS:

CHANGING ADMINISTRATION SETS LESS FREQUENTLY:

The package insert of propofol (Diprivan) recommends that “the tubing and any unused DIPRIVAN Injectable Emulsion drug product should be discarded after 12 hours because DIPRIVAN Injectable Emulsion contains no preservatives and is capable of supporting growth of microorganisms.”\textsuperscript{1} Recently, the Infusion Nurses Society (INS) addressed Frequently Asked Questions Related to COVID-19 Health Care Challenges. INS states that there is “no supportive evidence that enables INS to change the timeliness recommended in the Infusion Therapy Standards of Practice for administration set changes. Recommendations for propofol infusions align with package inserts to change set frequency every 6 to 12 hours.\textsuperscript{21}

POOLING PROPOFOL:

Propofol's lipid base supports microbial growth. The manufacturer labeling for propofol contains warnings for inadvertent microbial contamination causing “fever, infection, sepsis, other life-threatening illness, and death.” An additional warning states there have been reports of bloodborne diseases being transmitted due to unsafe injection practices. Strict aseptic technique is recommended for handling. While propofol formulations do contain antimicrobial agents, these agents only inhibit the growth of microorganisms for up to 12 hours, and propofol products are not considered antimicrobi ally preserved under USP standards. Per the labeling, administration must be completed within 12 hours of spiking the vial, and any unused product must be discarded. The tubing must also be discarded after 12 hours. The same requirements apply if propofol is transferred to a syringe prior to administration.\textsuperscript{1-8} U.S. labeling does not provide additional beyond-use recommendations for diluted propofol, but Canadian labeling recommends diluted propofol not be used beyond 6 hours after preparation.\textsuperscript{11}

Propofol products are labeled as single access or single patient vials.\textsuperscript{1-5} The current version of USP <797> (last revised in 2008) requires a BUD of 6 hours, unless specified otherwise by the manufacturer, for single-dose containers in ISO Class 5 or cleaner and a BUD of 1 hour for single-dose containers opened or entered in worse than ISO Class 5 air.\textsuperscript{12} The proposed version of USP <797> (last revised in 2019) states a single-dose vial entered in ISO Class 5 or cleaner may be used for up to 12 hours as long as storage requirements are maintained throughout the 12-hour period.\textsuperscript{13}

Due to the number of potential components (>3) involved in this preparation, compounding would ideally occur in an ISO 5 primary engineering control that is located in an ISO 7 buffer area to prevent exposure to microbial contamination. Current USP guidance would consider this a medium-risk compounded sterile product and could therefore receive a 30 hour BUD at room temperature.\textsuperscript{12} Under the proposed USP <797> guidance, which some states have adopted, this may differ.\textsuperscript{13} Although in the case of propofol, the final BUD
should be based on manufacturer labeling for each presentation due to product variability (6-12 hours) as discussed previously.

The final container should minimize the risk of degradation and microbial contamination. Sterile empty containers should be utilized. Glass, PP, and polyolefin containers are preferred over PVC containers.

REFERENCES

16. Diprivan® (propofol), injectable emulsion, USP: stability and compatibility in plastic bags. Fresenius Kabi USA, LLC.