SAFETY OF PARENTERAL INFUSIONS IN THE CRITICAL CARE SETTING*

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Abstract

Maintaining proper dosage and overall integrity of pharmaceuticals administered to critically ill patients is essential to ensuring effective treatment and care. The fragility of the intensive care patient heightens the need for physicochemical stability and compatibility of intravenous formulations. This article defines the major stability, compatibility, and sterility characteristics of the most commonly used sedatives and offers recommendations for the clinician for maintaining their effectiveness and safety through proper aseptic technique and procedure.

*This article is based on a presentation given by Dr. Driscoll at a satellite symposium held at the Society of Critical Care Medicine, January 27, 2002.

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Efficacious delivery of drugs is a key component in the successful treatment of critically ill patients. However, the benefits of optimal clinical care can be lessened by poor production or manufacturing processes at the industrial level or by the application of poorly executed extemporaneous compounding of parenteral dosage forms. While manufacturing processes are tightly controlled by regulatory authorities, further compounding and preparation of these commercial dosage forms often occur either at the pharmacy level or by nonpharmacists in the critical care setting. Thus, a variety of pharmaceutical factors may affect the dosage form integrity with respect to stability, compatibility, sterility, dosing, and packaging.

Required Physicochemical Characteristics of Intravenous (IV) Dosage Forms

The fragility of the intensive care unit (ICU) patient accentuates the importance of the physicochemical stability and compatibility issues in intravenous formulations. The critical characteristics necessary to safely provide intravenous therapy include:

- Miscible with blood: Because blood has more aqueous than nonaqueous characteristics, an infusion product must be water soluble for IV administration. Poorly water-soluble substances can be given intravenously if a more stable preparation of the drug is modified, such as incorporation into emulsified oil droplets dispersed in sterile water, or as liposomal drug delivery systems.
- Free of infectious contaminants: While industrial manufacturing of IV drugs is tightly regulated, products made extemporaneously by clinicians are often managed by institutional policies recognizing that the final dosage form must also be sterile and pyrogen free, and thus used with great care. Ideally, aseptic technique should be accomplished within the sterile environment of a Class A laminar airflow hood. While these hoods are...
routinely placed in pharmacies, they also can be located in emergency rooms or near operating rooms. However, they are rarely, if ever, located directly in the ICU setting.

- Free of particulate matter: Particles may be noninfectious, yet large quantities may pose clinically significant issues, ranging from superficial peripheral vein phlebitis to fatal pulmonary embolism. Risks are reduced in the critical care setting when extemporaneous manipulation of the original infusion container is conducted within the confines of a laminar hood, and through use of an in-line filter during infusion.

- Stable for a defined period of time: The expiration date of the commercial product, assigned by the manufacturer, ensures its integrity when stored as recommended by package insert. However, once opened for clinical use, the manufacturer-assigned expiration date becomes null and void, and a beyond-use date must be assigned to the final dosage form according to additional information in the package insert and/or peer-reviewed literature sources. The product must be stable throughout its shelf life, and acceptable beyond-use limits are imposed once the container has been opened.

Pharmaceutical issues that will ensure infusion safety include stability, compatibility, sterility, and dosing that is appropriate to the condition.

**Stability**

The stability of any drug or dosage form may be affected by the characteristics of its container or packaging and the temperature of the ambient space. The United States Pharmacopeia (USP) sets standards for drug purity and safety in the United States, and is regulated by the Food and Drug Administration (FDA).

The USP makes a clear distinction between expiration date and beyond-use date. The expiration date, assigned by the manufacturer, limits the time during which the drug may be dispensed and is based on stability studies that have been reviewed by the FDA. Beyond-use dates are affixed by the pharmacist and are in force once the packaging is opened or violated by a needle and, thereby, exposed to ambient atmospheric conditions. Once the packaging has been opened, the expiration date is replaced by a documented beyond-use date. When applied to products delivered by infusion, the beyond-use date often is a matter of hours or days after the container has been opened. Stability can be ensured with the assignment of a rational beyond-use date that is verifiable and then optimized to the patient and condition.

**Compatibility**

Packaging is important in the determination of a rational beyond-use date. A certain quantity of drug may be lost through sorption by plastic containers used for infusion. Many drugs, such as benzodiazepines, are lipophilic substances that can penetrate the plastic matrix of the infusion container, resulting in subtherapeutic dosing. The comixing of multiple drugs in a single container, or the addition of a single drug in a common IV diluent (eg, 5% dextrose in water, normal saline, or Lactated Ringers), may result in an incompatibility (coprecipitate of 2 or more drugs or “salting out” of a single drug) that may be clinically significant or dangerous if infused into the systemic circulation.

**Sterility**

The application of aseptic technique is imperative and must be closely observed in nonpharmacy settings. An essential first step is hand washing with an antiseptic; use of isopropyl alcohol wipes to disinfect rubber stoppers is likewise important. Lack of aseptic technique can lead to contamination. Investigations into the practices of clinical personnel in 7 hospitals revealed multiple breakdowns in aseptic technique.

**Dosing**

An appropriate dose is the amount infused that produces the desired clinical response. The actual dose is the amount expected to be delivered commensurate with the assigned beyond-use date. According to USP standards, a typical single dose must contain plus or minus a predetermined quantity of the labeled amount. This quantity is largely based on the therapeutic index of a given drug, with smaller variances for potentially toxic drugs and higher variances for less toxic medications. A common “quantity” for many drugs is ±10% of the labeled amount. The USP-assigned “quantities” have not yet been established for midazolam and propofol, but diazepam, lorazepam, and haloperidol must be in accordance with ±10% standard of the labeled amount.

In determining safely compounded intravenous drug formulations, the following documentation should be considered when reviewing literature that
reports on data about a drug outside of the FDA-approved manufacturer's package insert:

- The method of analysis is stability indicating, ie, able to differentiate between the parent compound and any degradation products.
- Time-zero concentration is reported. The amount reported on the label must be verified; any drug report without a time-zero concentration should not be regarded as a credible reference source.
- If criteria have been determined by the USP, the drug must accord with those established reference criteria (such as ±10% of the labeled amount) at each interval.
- The reference study used must simulate actual conditions of clinical use, not laboratory use.
- If lipids are involved, the stability of the emulsion also must be assessed, in addition to the active drug.

**Drugs Recommended for Use in ICU Sedation**

**Midazolam**

Stability: Midazolam is a moderately hydrophobic drug and is highly dependent on the pH of the final solution; it is acidic, with a pH of approximately 3.0.

Compatibility: The aqueous open-ring structure allows for compatibility. As the pH rises, the closed ring forms and can cause incompatibility. A 1992 study that adjusted the final admixture pH to 7.0 resulted in 64% of the drug absorbed into the container within 24 hours, and hence, less than half of the intended dose would be administered under these conditions, and might assume clinical significance. Thus, the pharmaceutical and clinical efficacy of midazolam is highly dependent on the pH of the media in which it resides. In the vial, the drug is specially buffered in the acidic range that promotes the aqueous open-ring structure and creates ideal conditions for shelf life. However, at physiologic pH (7.40), the open-ring is replaced by the closed-ring form that allows penetration of the blood-brain barrier to exert its pharmacological effects. Thus, prior to infusion, an open-ring structure is desirable for efficient drug delivery.

Sterility: No difference from other aqueous parenteral solutions.

Dosing: Intermittent—0.02-0.08 mg/kg; Infusion—0.04-0.20 mg/kg/h.

**Diazepam**

Stability: Diazepam is considered extremely hydrophobic, with no significant changes in stability under normal conditions of use. In general, it should not be mixed with other medications.

Compatibility: Benzodiazepines contain a complex cosolvent system that creates solubility issues in dilute infusions. As the concentration of the cosolvent system decreases upon dilution, the drug begins to precipitate. Significant sorption losses of up to 90% in a 24-hour period are due to its highly lipophilic nature.

Sterility: No difference from other aqueous parenteral solutions.

Dosing: Intermittent—0.03-0.10 mg/kg; infusion is not recommended.

**Lorazepam**

Stability: Lorazepam is mildly hydrophobic, with no significant changes under normal conditions of use.

Compatibility: Like other benzodiazepines, sorption is problematic. Losses range from 0.7% to 29% in a 24-hour period. Because it has a cosolvent system, solubility issues exist when lorazepam is diluted from its original container.

Sterility: No difference from other aqueous parenteral solutions.

Dosing: Intermittent—0.02-0.06 mg/kg; infusion—0.01-0.10 mg/kg/h.

**Propofol**

Stability, compatibility, and sterility issues all must be addressed in accordance with both the drug itself and the vehicle, an oil (10% soybean oil) in water emulsion.

Intermittent dosing is not recommended; infusion dosing of the drug is 0.3-5 mg/kg/h and of the emulsion is <0.11 g/kg/h.

**Emulsions**

The first lipid emulsion available in the United States was composed of long-chain triglycerides (LCT) made from cottonseed oil and a mixture of natural and synthetic emulsifying agents, but was banned by the FDA in 1964 due to severe side effects. A safer soybean oil-egg yolk phospholipid LCT emulsion has been commercially available since 1978 and is now used routinely. Long-chain triglyceride emulsions are clinically beneficial as they are calorically dense and can be given safely through a peripheral vein. However, if misused, they are associated with numerous adverse
events, including impaired immune, pulmonary, hepatic, and platelet function.4

**Drug Emulsion Stability and Compatibility**

Instability of emulsions is the reversion of the homogeneous mixture back to its original 2 phases of oil and water. All emulsions will revert over time, although the rate of instability is variable and dependent upon several factors. The composition of the oil phase, extemporaneous compounding practices, and end-user conditions have a significant effect on emulsion stability and safety. As physicochemical barriers against instability degrade, the homogeneous distribution of the lipid droplets is disrupted, and coalescence occurs with the formation of enlarged fat globules that may assume clinical significance upon infusion. Once the volume-weighted percentage of fat globules greater than 5 microns in size exceeds 0.4% of the total fat present, free oil is often seen, signaling an unstable and potentially dangerous IV formulation.1

One of the most significant toxic effects of an unstable or incompatible emulsion is a plasma-derived fat embolism.5 If drug emulsions become unstable, the once homogeneous distribution of lipid droplets and the drug contained therein is disrupted and may lead to either therapeutic failures or clinical toxicity. The combination of a fat embolism and inhomogeneous drug delivery can act synergistically and result in a potentially lethal event. The Figure illustrates an example of an emulsion that destabilizes over time.

**Drug Emulsion Sterility and Dosing**

Sterility issues with emulsions are heightened compared with aqueous parenteral infusions, as IV lipid emulsions have a median pH of approximately 7.5 (range: 6.0-9.0), an osmolality between 250 mOsm/L and 350 mOsm/L, and contain between 2.25% and 2.5% glycerol, all of which are conducive to bacterial growth.6 Thus, great care in the preparation and dispensing of the final dosage form is absolutely necessary to ensure a safe infusion.

The dosing issues of the emulsion vehicle may cause lipid intolerance related to an excessively high lipid infusion rate; a suboptimal phospholipid-triglyceride ratio that may impair fat clearance; underlying hypertriglyceridemias; and disregard of lipid from the nutrition therapy.

**Propofol 2%: Effect on Lipids**

A more concentrated preparation of propofol has been developed, but is not yet available in the United States. A 2% propofol (20 mg/mL) dosage form presents half the usual lipid load to critically ill patients and reduces the volume of drug necessary by half, compared with presently available propofol 1% formulations. While infusions of propofol 1% given with parenteral nutrition–containing lipid have been associated with a 4-fold increase in triglycerides after 10 days, infusion of propofol 2% over a 50-hour period did not result in a significant increase in triglyceride concentrations. Cholesterol and high-density lipoprotein-
tein concentrations were at the low end of the normal range, and peak triglyceride concentrations were only mildly increased (>3 mmol/L). 7

**PRINCIPLES OF INFUSION SAFETY: EMULSIONS**

When considering beyond-use dates in the preparation of parenteral infusions, only the drug and infusion components must be taken into account, whereas for drug emulsions, the vehicle also must be considered. That is, the stability of the emulsion assumes equal importance to the drug in the safety of the infusion. An unstable emulsion vehicle will affect the therapeutic response, even though the drug remains stable, as the uniformity of the drug delivery system is disrupted. Nevertheless, lipid emulsion drug vehicles offer significant pharmaceutical and pharmacokinetic advantages not obtainable in conventional aqueous infusion systems.

Emulsions have unique considerations with respect to the application of aseptic technique during drug preparation. Their high pH, isotonicity, and inclusion of glycerol allow for the exuberant growth of many microorganisms, and heighten the need for extreme care during clinical use. This is especially true when drug emulsions are prepared outside a certified laminar airflow environment, such as at the patient's bedside. The significance of this fact is evidenced in the package inserts of propofol dosage forms. Despite the presence of microbial retardants, once a single-dose unit of propofol is opened, the beyond-use date is 12 hours; however, if the drug is removed from its original container and provided in a syringe delivery system, the beyond-use date is reduced to 6 hours. Thus, in the present case, use of an alternative drug container reduces the beyond-use date by 50%.

**CONCLUSIONS**

The clinician must strive to ensure infusion safety through adherence to expiration and beyond-use dates, aseptic technique, and consideration of stability, compatibility, sterility, and dosing issues.

Recognizing the differences between pharmacy and nonpharmacy practices, emulsions create unique safety issues, particularly in the ICU where the margin of error is narrow and adverse patient events are magnified.

**REFERENCES**