ISMP Medication Error Report Analysis

Understanding and Managing Intravenous Container Overfill Potential Dose Confusion

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These medication errors have occurred in health care facilities at least once. They will happen again—perhaps where you work. Through education and alertness of personnel and procedural safeguards, they can be avoided. You should consider publishing accounts of errors in your newsletters and/or presenting them at your inservice training programs.

Your assistance is required to continue this feature. The reports described here were received through the Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program. Any reports published by ISMP will be anonymous. Comments are also invited; the writers' names will be published if desired. ISMP may be contacted at the address shown below.

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UNDERSTANDING AND MANAGING INTRAVENOUS CONTAINER OVERFILL

In August 2013, ISMP Canada issued a *Safety Bulletin* describing an incident in which more than 1,100 patients in Canada received more dilute, and therefore less potent, chemotherapy solutions than intended. Larger bags of chemotherapy had been used to prepare smaller individual doses of chemotherapy, but overfill in the bags used to prepare and administer the chemotherapy was not understood or managed.¹ Management of overfill volume is critical for chemotherapy, because dosing is specific to each patient and the type of cancer being treated. Not surprisingly, patients or family members who were contacted about receiving lower chemotherapy doses were concerned about the effects of the error. Although the overall impact on patients was felt to be low,² some family members who had recently lost loved ones asked whether the error might have contributed to a premature death. Family responses to disclosure of the error were particularly emotional when the cancer victim was a child.³

About the Event

A group purchasing organization contracted with a new compounding pharmacy to provide cyclophosphamide and gemcitabine solutions to hospitals. These drugs were used as part of regimens to treat various solid tumor malignancies, lymphoma, and leukemia in adults and children. A discrepancy in labeling on a gemcitabine preparation between the previous supplier and the new supplier led a hospital pharmacist to ask the compounding pharmacy for clarification. It then became apparent that there was a misunderstanding about how the compounded solutions were being used by the hospitals. The new compounding pharmacy thought that each full bag of gemcitabine and cyclophosphamide contained a single dose to be administered to a single patient. However, the hospitals were using each bag as a multidose product, apportioning the medication from a single bag among several patients. Believing each bag was a single dose, the compounding pharmacy did not account for the volume of overfill in the bag when labeling the concentration of the prepared product.

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Although the full dose in each bag was listed on the label, the actual concentration of the drug (mg per mL) in each bag was lower than stated due to overfill in the normal saline bags used to dilute the medication. The best estimate is that the average actual cyclophosphamide concentration was 10% lower than stated on the label, and the average actual gemcitabine concentration was 7% lower than stated on the label.

Overfill in Commercial Containers

Although a commercially available bag or bottle of parenteral solution may be labeled to contain 25, 50, 100, 250, 500, or 1,000 mL, the actual volume is larger because it contains overfill. The containers may be permeable to oxygen and experience a loss of water (evaporation through plastic) to some extent, depending on the storage conditions, specific contents, permeability of the container, and ratio of fluid volume to the container surface area. Thus, there is some variability in the targeted amount of overfill specified by each manufacturer in each bag, as well as variability in the contents of any bag at any point in time. Despite this variability, vendors of solutions can provide customers with a targeted amount and range of overfill in each of their products.

Preparation Effects on Final Volume and Concentration

In general, the preparation of a compounded medication infusion involves diluting the drug with a diluent (eg, sterile water) and transferring the prescribed amount of drug into a final dosage container (eg, empty sterile syringe, small volume parenteral solution bag, large volume parenteral solution bottle). In practice, there are several different practitioner-based and manufacturer-based preparation methods. The preparation method used affects the total volume and concentration of the final product.

Practitioner-Based Methods

1. *Adding to a commercial container (simple admixture).* The prescribed medication is added to a manufacturer's base solution container, such as 0.9% sodium chloride, in an intravenous (IV) bag without concern for overfill. This is typically used for the admixture of intermittently administered solutions when the entire bag is intended to be infused to a single patient over a short time (eg, 30 minutes). This method may also be used to prepare medications administered via continuous infusion when the slight difference in per mL concentration may not be as important because the effect of the medication is being continuously monitored (eg, diltiazem infusion).
2. *Withdrawal prior to admixture (drug volume).* A volume of the base solution equal to the volume of the medication to be added to the container is withdrawn from the manufacturer's container, without concern about overfill. The medication is then added to the remaining volume in the container. This method is typically used when the volume of medication to be added is large relative to the size of the base solution container. For example, before adding 150 mL of sodium bicarbonate from a syringe or vial to a 1,000 mL bag of dextrose 5%, a volume of 150 mL of the base solution is withdrawn from the bag and discarded.
3. *Withdrawal prior to admixture (drug volume and overfill volume).* A volume of the base solution equal to the sum of the volume of the medication to be added to the container and the estimated volume of overfill is withdrawn from the manufacturer's container. The medication is then added to the remaining volume in the container. This method is typically used when the volume of medication to be added is large relative to the size of the base solution container.
4. *Starting with an empty container (full sterile compounding).* The measured amount of medication and base solution are added to an empty IV bag or other container. With this method, there is no overfill. This method may be used when both the total amount of drug in the final container and the concentration of drug need to be precise and must be accurately known. The final container can be labeled with a specific drug concentration (mg/mL).

With the first 3 practitioner-based methods, the total dose of the medication is known, but the concentration cannot be calculated accurately because the volume of overfill of the base solution is not exactly known but can only be estimated. The final container should not be labeled with a specific concentration per mL because of the unknowns. The pharmacist may or may not add more drug to offset the overfill volume. These bags should only be labeled with the total amount of drug in the container and the total estimated volume. Only with method 4 can the concentration (mg per mL) be accurately calculated and added to the pharmacy label.

Manufacturer-Based Methods

1. *Drug plus overfill.* A medication for parenteral use is manufactured in large quantities to a specific concentration (eg, mg/mL). The required volume of this solution, in addition to the overfill containing the medication at the same concentration, is added to an empty parenteral container. This method is used for commonly manufactured premixed solutions approved by the US Food and Drug Administration (FDA). With this method, the medication concentration in the container (drug per unit volume) at the time of manufacture is the same as the concentration on the label. However, the final product contains more volume than the label indicates due to overfill. For example, an IV bag of gentamicin labeled as containing 80 mg/100 mL contains the labeled 80 mg and another 4 mg of the drug in the 5 mL of overfill.
2. *Compounding pharmacy methods.* A supplier (eg, compounding pharmacy) may use any of the practitioner-based methods or the manufacturer-based method described above to prepare individual doses of IV medications.

Other Risk Factors to Consider

Variables related to other processes with medication use can also affect the actual dose delivered to the patient (see **Table 1**). In particular, variability in admixture practices within a single hospital and among the same drug infusions can result in dosing inconsistencies and errors—as it did in the tragic death of Emily Jerry, whose chemotherapy was

prepared using one method but was assumed to be prepared using another method.⁴ Many nurses are unaware of the potential overfill in an infusion bag or bottle and may stop the infusion of an intermittent dose of medication as soon as the stated volume (eg, 150 mL) has been infused, as programmed in an infusion pump. Further, nurses who recognize that overfill might be present in a pharmacy-prepared infusion bag or bottle have often misunderstood the “extra” solution as a pharmacy accommodation for the amount of drug lost in the tubing. Thus, the 20 to 25 mL of solution in pump tubing sets, which may account for a significant portion of the total dose, will not be received because the bag would not be completely infused.

Health care organizations must develop standardized preparation methods that are appropriate for various clinical situations. When doing this, it is important to balance the benefits of process changes against additional risks that such changes may present. In particular, changes that increase the manipulation of products or the complexity of processes can pose new risks that outweigh the benefit of added dosing accuracy. There is no single, standard method appropriate for all infusions in all hospitals, particularly given the variability in environmental conditions, staff expertise, and technology among hospitals. However, consider the following points when designing processes in your hospital for admixture and sterile compounding.

- **Clearly define processes.** Choose the most appropriate method of preparing each medication infusion according to whether or not the volume (and

Table 1. Sources of dose variability

Source of variability	Description of variability
Manufacturer	<ul style="list-style-type: none"> • Regulations allow variances in manufactured doses of medications. • Overfill volumes vary among manufacturers. • Amount of evaporative fluid loss may vary from one IV bag to another.
Medication preparation	<ul style="list-style-type: none"> • Admixture practices may vary among practitioners or facilities.
Medication administration	<ul style="list-style-type: none"> • Different administration practices (eg, medication remaining in IV tubing; pump alarm stoppages).
Equipment	<ul style="list-style-type: none"> • Regulations allow variances in the volume infused by infusion pumps. • Disposable syringes may not be calibrated exactly.
Prescribing	<ul style="list-style-type: none"> • A patient's weight may fluctuate, affecting weight-based dosing. • The practices, processes, and equipment used to determine a dose in a clinical trial may differ from the practices, processes, and equipment used in a particular environment.

therefore the concentration) is critical. Start by developing a list to identify medications and situations for which added accuracy in dose or concentration is needed and the level of accuracy required. This list will help determine which preparation method should be used for specific drugs. Also, obtain a list of overfill amounts of commonly used products from vendors for reference as necessary.

- **Continuous infusions.** Medications administered by continuous IV infusion are typically titrated to a desired effect (eg, pain relief with opioids, blood pressure control with vasopressors, anticoagulation with heparin). Thus, the key strategy with these infusions is to ensure consistency in the preparation process in order to avoid variations in concentration and inconsistencies with the dose delivered. In these instances, a standard process for simple admixture may be all that is needed to ensure consistency from bag to bag and the desired therapeutic effect.
- **Intermittent single doses.** For a single-dose drug infusion, the most critical aspect of the process is ensuring that the entire dose in the container is administered. Thus, the product label must be explicit regarding how to deliver the entire dose, which is dependent on the preparation process. For example, if 160 mg of carboplatin has been added directly to the IV bag without withdrawal of any solution before admixing, the label should read as follows:

CARBOPlatin 160 mg (16 mL) +
0.9% Sodium Chloride (100 mL) +
OVERFILL (7 mL) = 123 mL total
Infuse entire contents for full dose

For infusions in which the dose remaining in the tubing must also be infused to deliver the entire dose (eg, chemotherapy, neonatal medications), the product label should specify that the tubing should be flushed with a particular diluent and volume. When the rate of administration is critical, as for some IV medications given intermittently by infusion pump, ensure that information about the rate of administration and flush is built into relevant protocols and smart infusion pumps.

- **Prepared medications intended for multiple doses.** The preparation of medications for multiple doses (eg, bulk preparation) ideally requires full sterile

compounding of the product. Bags containing the manufacturer's base solution contain a variable amount of overfill, and specific concentrations of drugs can be prepared only by starting with an empty bag or other container. Keep in mind that an error occurring early in the process (eg, during medication reconstitution) may have an impact on the dose of medication received by multiple patients. Therefore, pharmacies that prepare IV medications intended for multiple doses should proactively evaluate their processes and take necessary precautions to mitigate identified risks. (See ISMP compounding guidelines at: www.ismp.org/sc?id=264.)

- **10% rule.** The 10% rule is used by some hospitals during the preparation of infusions to determine whether fluid should be removed from the bulk solution container prior to the addition of the medication. The rule suggests that if the volume of the additive medication(s) is more than 10% of the volume listed on the bulk solution container (without regard to overfill), the volume of the additive, and sometimes the volume of the overfill, will be removed. Unless starting with an empty bag (full sterile compounding), the 10% rule is often applied to all admixtures, except small volume intermittent solutions such as antibiotics or other products with manufacturer-specified preparation procedures. Whatever method is chosen, it is critical to be consistent within your organization.
- **Guide the processes.** Develop protocols that specify how drug infusions should be prepared. Consider using compounding worksheets to guide the procedures for making common infusions. (In the United Kingdom, for example, a predesigned worksheet is used to ensure admixtures are prepared to exact specifications, thus standardizing the processes. This also provides documentation of compounded products.)
- **Specify on labels.** Design labels with the end user in mind. In situations where either the dose or the timeframe over which the dose is to be administered is critical, the information about dose, total volume, and concentration that appears on the label should be designed to guide the processes for administration, including the use of infusion pumps. These labels should include the total amount of drug in the total volume of solution. If the entire contents of the container must be administered to provide the specified dose, the label should also include a reminder: Infuse entire contents for full dose.

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POTENTIAL DOSE CONFUSION

Communicating the proper dose of *Spiriva* (tiotropium) can be difficult with many computer order entry systems. *Spiriva* is an oral inhalation

product indicated for the long-term maintenance treatment of bronchospasms associated with chronic obstructive pulmonary disease (COPD). The product comes with a HandiHaler device intended to deliver the full contents of the drug, which is contained in a capsule for inhalation. The recommended dose of *Spiriva*, using the HandiHaler, is 2 inhalations of the powder contents of 1 capsule. Many computer order entry systems will default to a dose of 1 inhalation. If you change the default value to 2 inhalations, confusion can lead to the patient receiving the contents of 2 capsules. If you enter 1 capsule, the patient may receive the product orally. Ideally, the dose should be expressed in a way that makes it clear (eg, 1 capsule = 2 inhalations).

Make sure the dosing for *Spiriva* is expressed clearly in your order entry system to avoid administering the wrong dose or via the wrong route, by which the patient may take the capsule orally rather than piercing it in the HandiHaler and inhaling its contents. Ensure the patient is educated about and understands how to properly use the medication and device. ■