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A KEY PARTNER IN
CMIRPS Canadian Medication Incident Reporting and Prevention System
SCDPIM Système canadien de déclaration et de prévention des incidents médicamenteux

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Managing Overfill during Preparation and Delivery of Intravenous Medications

Earlier this year, it was discovered that a number of patients with cancer had received more dilute, and therefore less potent, chemotherapy solutions than intended due to the presence of overfill* in the intravenous (IV) bags used to prepare and administer the chemotherapy drugs.[1] This incident has been the subject of intense scrutiny, and the findings of a formal review (which readers are encouraged to read) have recently been released.[2] As a result of the incident, attention has been drawn to the processes for preparing and labelling IV medications and to the management of overfill of the base solution (e.g., 0.9% sodium chloride) in IV bags purchased from manufacturers. This bulletin highlights variables in the medication-use process (especially during medication preparation) that may affect the total dose or concentration of medication delivered and provides interim guidance to healthcare facilities with examples of when and how to incorporate overfill into existing processes.

Medication Incident

A group purchasing organization awarded a contract to a new supplier for the provision of admixed cyclophosphamide and gemcitabine to hospitals. A discrepancy in labelling for the gemcitabine preparation between the previous supplier and the new supplier led a hospital to ask the new supplier for clarification. It then became apparent that there was a misunderstanding about how the medication was being used. The new supplier was expecting that each full bag would be administered to a single patient when the hospitals covered by the supplier contract were using each gemcitabine bag as a multidose product (i.e., a reconstituted medication solution), apportioning the medication from a single bag among several patients.

Methods of Preparing IV Medications and Effects on Final Volume and Concentration

In general, the preparation of an IV medication involves diluting the drug with a base solution (e.g., 0.9% sodium chloride) in an IV bag. In practice, there are several different preparation methods (practitioner-based and manufacturer-based methods described below). The preparation method used affects the total volume and concentration of the final product.

Practitioner-based methods

1. A medication for IV use is added to a manufacturer's IV base solution product (e.g., 0.9% sodium chloride in a bag). This is the

* The bags used for intravenous (IV) administration of drugs are made of material that allows the solution contained inside to evaporate during storage. A small volume of solution, called overfill, is added to the IV solution bags at the time of manufacture to ensure that the bag contains the labelled volume at the expiry date. As noted by reviewers of this bulletin, the overfill volume can also allow for priming of IV lines. The amount of overfill added is based on the type of solution and the size of the bag.

simplest preparation process that can be used by practitioners (e.g., front-line nursing and pharmacy staff), typically for the admixture of intermittently administered solutions (i.e., when the entire bag will be infused to a single patient over a short period of time [e.g., 30 minutes]). This method may also be used for medications administered by continuous infusion. The final volume consists of the combined volume of the manufacturer's IV base solution, the overfill volume added by the manufacturer, and the volume of the medication.

2. In a second method, a volume of the IV base solution equal to the volume of the medication to be added to the IV bag is withdrawn from the manufacturer's IV base solution bag. The medication is then added to the remaining volume in the IV bag. This method is typically used when the volume of medication to be added is large relative to the size of the IV bag. For example, before addition of 150 mL of sodium bicarbonate IV solution for injection to a 1000 mL bag of dextrose 5%, a volume of 150 mL of the base solution is withdrawn from the bag. The final volume in a bag prepared by this method consists of the combined volume of the manufacturer's IV base solution (after removal of a volume equal to that of the medication to be added), the overfill volume added by the manufacturer, and the volume of the medication.

   Note: With each of these 2 practitioner-based methods, the total dose of medication is known, but the concentration cannot be calculated because the volume of overfill of the IV base solution is not known.

3. A third method involves adding the medication and IV base solution to an empty IV bag. With this method, there is no overfill. This method may be used when both the total amount of drug in the IV bag and the concentration must be accurately known.

Manufacturer-based methods

1. A medication for IV use is manufactured in large quantities to a specific concentration (amount of drug per unit volume [e.g., millilitre] of solution). The required volume of this solution, in addition to overfill containing the medication at the same concentration, is added to an empty IV bag. This method is used for commonly manufactured premixed medications approved by Health Canada.

   Note: With this method, the medication concentration in the bag (amount of drug per unit volume) at the time of manufacture is the same as the concentration appearing on the label. However, the final product contains more drug than the label indicates due to overfill. For example, a bag labelled as containing 20 mmol of potassium chloride in 100 mL contains the labelled 20 mmol plus the amount of potassium chloride in the overfill volume.

2. A supplier (e.g., a compounding company) may use one of the three practitioner-based methods described above to prepare individual doses of IV medications.

Next Steps

The choice of preparation method for any admixed IV product affects the total dose of drug and its concentration in the IV bag. Healthcare organizations must develop approaches to determine the best preparation method for various situations. To further complicate matters, variables related to other processes within the medication-use system (e.g., medication administration) can also confound or offset the variances generated during dose preparation, further affecting the actual dose delivered to the patient. Table 1 highlights the sources of variability within the medication-use system.

With this broader view of the variabilities in medication dosing in mind, it is important to balance the benefits of process changes against any additional risks that such changes may present to patients. In particular, changes that increase the manipulation of products or the complexity of processes can pose new risks that may outweigh the benefit of added accuracy in dosing.

In situations where either the dose or the timeframe over which the dose is to be administered is determined to be critical, then the information about

Table 1: Examples of Sources of Variability in Medication Doses Received by Patients

Source of Variability	Description of Variability
Manufacturer	• Regulations allow for variances in manufactured doses of a medication. • Overfill volumes vary among manufacturers. • Amount of evaporative fluid loss may vary from one IV bag to another.
Medication preparation	• Admixture practices may vary among practitioners or facilities.
Medication administration	• Individual practitioners use different administration practices (e.g., for management of "dead volume", the medication that remains in IV tubing).
Equipment	• Regulations allow for variances in the volume infused by infusion pumps (rate at which medication is administered). • Most large-volume infusion pumps are unable to recognize primary and secondary infusions as separate entities and rely on gravity principles to determine which source the pump will draw from.*
Prescribing	• A patient's weight may fluctuate, which will affect weight-based dosing. • For some drugs, the dose for a particular patient is selected from a dose range. • The practices, processes, and equipment used to determine dose administration in a clinical trial may differ from the practices, processes, and equipment used in a particular practice environment.

* Setting the total volume of a secondary infusion that is to be infused will not prevent the pump from drawing additional volume from the secondary bag. In other words, if the fluid level in the secondary bag is at a height above the fluid level of the primary bag, the pump will continue to draw from the secondary source.

dose, volume, and concentration that appears on the label should be designed to guide processes for administration (including use of equipment such as infusion pumps).

Recommended Practices

For Medications Administered by Continuous IV Infusion

Medications administered by continuous IV infusion are typically titrated to a desired effect (e.g., pain relief with opioids, maintaining blood pressure with vasopressors, anticoagulation with heparin). To avoid variations in concentration (i.e., to ensure consistency in the dose delivered), it is important to ensure consistency in the medication preparation process from one bag to the next. Consistency is required regardless of whether the admixture is prepared within the pharmacy or when necessary, by a front-line practitioner in the patient care area.

- For admixtures prepared by practitioners, standardize the processes for preparing medications intended for continuous infusion. Clearly communicate these methods to help ensure that concentrations will be consistent regardless of personnel.

For Single-Dose IV Medications Administered Intermittently

For any single-dose medication, it is important that the specified dose be administered. In this situation, the directions for administration may vary depending on how the medication is prepared.

- When it is critical that the entire IV bag be administered, the product label should clearly specify this requirement. For example, if 160 mg of carboplatin has been added directly to the IV bag without withdrawal of any solution before admixing, the label could read as follows:

  Carboplatin 160 mg (16 mL) + 0.9% Sodium Chloride 100 mL + OVERFILL
  INFUSE ENTIRE CONTENTS FOR FULL DOSE

- 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 is built into relevant protocols, including smart infusion pumps.

For Prepared IV Medications Intended for Multiple Doses

The admixture of IV medications for multiple doses (e.g., bulk preparation) can create additional critical points for accurate medication dosing. For example, an error occurring early in the process (e.g., 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 consider proactively evaluating their processes and take any necessary precautions to mitigate any identified risks.

The following considerations increase complexity if multidose formats are being prepared:

- IV 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.
- Hospital-based formulas for multidose formats must incorporate appropriate dilution (based on the manufacturer's instructions for preparing drug ingredients that require reconstitution) to ensure accurate final concentrations. For example, 1 g vials of gemcitabine require dilution with 25 mL 0.9% sodium chloride to generate a final volume of 26.3 mL and concentration of 38 mg/mL.

Key Messages

- Identify specific medications and situations for which added accuracy in dose or concentration is needed and the level of accuracy required.
- Choose the most appropriate method of preparing each medication according to whether or not the volume (and therefore the concentration) is critical.
- Design labels with the end user in mind. Include information that has been determined to be critical and that will guide processes for administration.
- Variables related to other processes within the medication-use system (e.g., medication administration) can also confound or offset the variances generated during dose preparation, thereby affecting the dose delivered to the patient.
- Share this bulletin to communicate information about overfill and to alert practitioners about the variations that exist and the ways in which standardized processes within the practice setting can be designed to minimize variability.
- For hospitals that administer chemotherapy, consider completing the 2012 ISMP International Medication Safety Self Assessment for Oncology to heighten awareness of medication safety practices related to chemotherapy medications. For more information, visit: https://mssa.ismp-canada.org/oncology.
- Health Canada has met with ISMP Canada and will continue to engage in collaborative efforts to address issues associated with the labelling of IV bags.

Conclusions

The chemotherapy incident that has impacted many patients in Canada is being investigated by numerous committees and reviewing agencies. The report from the formal review in Ontario[2], released just recently, identified communication gaps about the presence of overfill in IV bags as one of the contributing factors to the incident. Heightened awareness of overfill in IV bags and of variability within the medication-use system offers opportunities for healthcare organizations to review their processes. Understanding the various methods of preparing IV medications is fundamental to identifying ways to optimize practices for the safe preparation, labelling, and administration of IV medications.

ALERT: **Drug Shortages Highlight the Need for Independent Double Checks**

ISMP Canada recently received a medication incident report describing errors in the revision of a master formula for total parenteral nutrition (TPN) at a healthcare organization that led to neonates receiving amounts of trace elements that were greater than intended. Trace elements are chemicals that the body requires in only minute amounts, including, for example, zinc, selenium, and manganese. In the incident reported to ISMP Canada, the healthcare organization had responded to a shortage of its usual zinc product by revising the TPN master formula to accommodate a new zinc formulation with a different concentration. Calculation errors were made during this process but were not discovered until a few months later. Fortunately, it appears that no adverse effects have occurred. The healthcare organization is conducting an extensive review to discover the underlying contributing factors.

ISMP Canada has previously reported on the value of independent double checks in reducing the risk of medication incidents.[1,2] Independent double checks have typically focused on high-alert medications; however this incident illustrates the value of such checks when alternative products (such as those with different doses or concentrations) are introduced into standard or established processes. The organization has distributed an interim safety alert to its practitioners about the merits of independent double checks based on previous ISMP Canada recommendations. The healthcare organization wanted to share this alert with other facilities to prevent a similar incident from occurring, especially given the current drug shortage situation, a setting in which the risk of a medication error is heightened.[2]

References

1. Lowering the risk of medication errors: independent double checks. ISMP Can Saf Bull. 2005 [cited 2013 July 3];5(1):1-2. Available from: http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2005-01.pdf
2. Drug shortages and medication safety concerns. ISMP Can Saf Bull. 2012 [cited 2013 July 3];12(3):1-4. Available from: http://www.ismp-canada.org/download/safetyBulletins/2012/ISMPCSB2012-03_Drug_Shortages.pdf

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References

1. Overfill needs to be taken into account for overfill chemotherapy. ISMP Can Saf Bull. 2013 [cited 9 Jul 2013];13(3):2. Available from: http://www.ismp-canada.org/download/safetyBulletins/2013/ISMPCSB2013-03_ReducingAdverseEventsWithDrugInteractions.pdf
2. Thiessen JJ. A review of the oncology under-dosing incident [report to the Ontario Minister of Health and Long-Term Care]. Toronto (ON): Ontario Ministry of Health and Long Term Care. 12 July 2013 [cited 11 Aug 2013]. Available from: http://www.health.gov.on.ca/en/public/programs/cancer/drugsupply/docs/report_thiessen_oncology_under-dosing.pdf

CMIRPS SCDPIM
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The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.

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The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

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