

Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Accidental overdoses involving fluorouracil infusions



PROBLEM: ISMP has received three reports of accidental overdoses with fluorouracil in 2015—two within the past 6 weeks. Approved more than 50 years ago, fluorouracil was one of the first intravenous cancer drugs and is still a mainstay in combination curative or palliative therapy regimens treating breast, colorectal, head and neck, gastric, pancreatic, anal, bladder, cervical, hepatobiliary, and esophageal cancers.¹ The National Institutes of Health reports that more than a quarter million Americans receive fluorouracil annually; of those, about 8,000 experience a toxic reaction, with some 1,300 patients dying each year from toxicity.^{2,3} Impaired clearance of the drug and medication errors are usually responsible for these adverse events.¹

The literature describes dozens of fluorouracil errors,^{3,4} and an international study of medication errors involving cytotoxic drugs between 1996 and 2008 found that fluorouracil was most commonly involved.⁴ Errors with fluorouracil are often caused by dose miscalculations, confusion between the dose per day and the total dose to infuse over multiple days, infusion pump programming errors, lack of pump programming safeguards, use of the wrong type of infusion pump in outpatient settings, failed independent double checks, confusing pharmacy labels, and lack of familiarity with the chemotherapy protocol.⁵

Report # 1

The most recently reported error with fluorouracil involved a young patient who received 4,500 mg of fluorouracil IV within 2 hours of starting the infusion, which was supposed to infuse over 46 hours. The patient had received 4,500 mg of fluorouracil via a new **CADD** ambulatory infusion pump that was connected and programmed in an outpatient oncology center. The CADD pump had been programmed incorrectly and delivered the full 2-day course of therapy over 2 hours. The patient was admitted to the hospital after a home care nurse noticed the error. The patient experienced toxic side effects including thrombocytopenia, myelosuppression, mucositis, edema of the hands and feet, arrhythmia, severe asthenia, and gastrointestinal effects. After being hospitalized for almost 2 weeks, the patient improved and was discharged to home.

Report #2

Last month, we learned about an error involving a patient who was to receive 4,000 mg of fluorouracil by IV infusion at 2 mL per hour over 4 days, but he accidentally received the entire 4-day dose in less than 1 hour. The error was caused by a mix-up between an **EASYPUMP** (B. Braun) elastomeric infusion pump that infuses 2 mL per hour with one that infuses 250 mL per hour (**Figure 1**). The Easypump, used mainly in the home, is available in 19 different volume and flow rate combinations for short- and long-



Figure 1. Easypump devices in 250 mL per hour (left) and 2 mL per hour (right) configurations. The flow rate marking, highlighted in yellow on both devices, was missed by several healthcare professionals who handled the pump.

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NPSF issues RCA guidelines

The National Patient Safety Foundation (NPSF) just released guidelines to help healthcare organizations improve the way they investigate errors, adverse events, and near misses. **RCA: Improving Root Cause Analyses and Actions to Prevent Harm** can be downloaded at: www.npsf.org/?page=RCA2. The guidelines will be discussed during a free webcast on **July 15**. To register, go to: www.npsf.org/events/event_details.asp?id=642263.

SAFETY briefs



Lack of e-prescribing interoperability leads to double dosing. A patient was being discharged from the hospital on warfarin 3 mg daily. The prescriber sent an electronic prescription (e-prescription) to the patient's outpatient pharmacy for warfarin, with instructions to take three 1 mg tablets daily. When the prescriber realized warfarin was available in a 3 mg tablet strength, he discontinued the first prescription and sent another e-prescription for one 3 mg tablet daily. The pharmacy received and dispensed both prescriptions to the patient. The patient took both, a total of 6 mg of warfarin, daily for several days before visiting an anticoagulation clinic where an elevated INR was measured and the error was discovered.

There were several contributing factors that led to this error. First, the prescriber did not realize that, with electronic prescribing (e-prescribing), discontinued orders are not transmitted to outpatient pharmacies. The prescriber must call the pharmacy to cancel the e-prescription. Next, the patient's medications were not reviewed with the patient before discharge. Although the patient was provided with a discharge medication list, the daily warfarin

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term infusions. The administration set and filter are already attached to the pump. Short-term infusions are often used to administer intermittent antibiotics, for example, while long-term infusions are often used to administer chemotherapy in the home. The pumps are packaged in outer cartons with labeling that is nearly identical, and the pharmacy technician choosing the device in the case above either did not know there was a difference between the pumps or overlooked the infusion rate because it is printed in a small size font on the front of the package (**Figure 2**). Although the device packaging notes pump flow rates in at least four places, none of the health professionals involved recognized they had a 250 mL per hour infuser in hand, instead of one that infuses 2 mL per hour. Fortunately, on the day the infusion started, the patient had an appointment for radiation therapy. A nurse there immediately recognized that there was no volume left in the pump and began to ask questions. The patient was admitted to a hospital, and treatment was begun using the antidote, uridine triacetate.

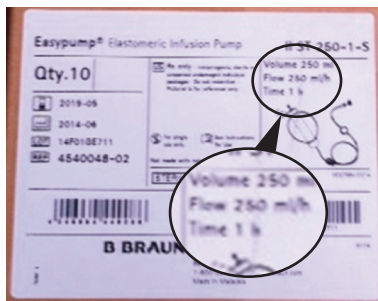
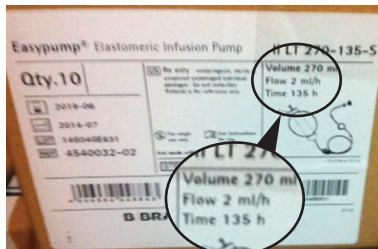


Figure 2. Flow rates on carton labels are difficult to identify.

We learned that the manufacturer uses color to differentiate the 19 different Easypump configurations, placing a color sticker on the pump administration set filter. Unfortunately, two of the configurations—the 2 mL per hour and 250 mL per hour pumps (**Figure 1**, page 1)—share a yellow-colored sticker. It is possible that the company allowed the shared color to be used given that one is a pump for long-term infusions, and the other a pump for short-term infusions. The company may not have realized that facilities might have both types of pumps. Incidentally, this event occurred when the hospital's supplying outsource pharmacy was notified of a shortage with their usual chemotherapy elastomeric pumps. As a result, they ordered the Easypump as a back-up, and thus, a pump with the wrong flow rate was used to deliver the fluorouracil infusion. We notified B. Braun, and the company responded immediately and agreed that labeling could be improved by using larger fonts to make the infusion rate stand out. Temporarily, a new yellow sticker with the infusion rate will be added to the carton to catch the user's eye. It may also be helpful to relocate the infusion rate label on the tubing closer to the pump so it is easily visible when holding the pump in the hand.

Report # 3

Earlier this year, we learned about another error in which the patient received a 5-fold overdose of fluorouracil. The recommended dose was 200 mg/m²/day continuous infusion for 5 days, but the oncologist wanted this treatment to infuse for only 100.5 hours (4.2 days), not a full 5 days (120 hours). Based on the patient's body surface area of 1.4 m², the pharmacist calculated the patient's daily dose to be 280 mg. He divided the daily dose by 24 hours to calculate an hourly dose of 11.66 mg, which he multiplied by 100.5 hours to obtain the correct course dose of 1,172 mg. He then erroneously multiplied that course dose by 5 days and prepared an infusion containing a total of 5,860 mg of fluorouracil to infuse over 100.5 hours. Although pharmacy policy required verification by another pharmacist of the patient-specific dose based on the mg/m² dose, the checking process was overlooked, and the infusion was dispensed. When the patient arrived in the oncologist's office to have the continuous infusion stopped and the implanted port flushed, staff noticed that the patient had re-

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dose was not specific and only stated to take the medication "as directed." It is uncertain whether the outpatient pharmacy computer system issued a duplicate therapy alert when the second warfarin prescription was entered. Also, the pharmacist did not question the two warfarin prescriptions or clarify the daily dose, perhaps believing that the 1 mg tablets were being provided for titration. However, the patient was never counseled when picking up the prescriptions.

Medications prescribed upon discharge must be one of the priorities requiring discharge education along with a clear demonstration of the patient's or caregiver's understanding. Consider giving patients discharged on warfarin a free educational leaflet on warfarin available from ISMP (www.ismp.org/ahrq/). The consumer leaflet will help patients understand proper medication use, how errors happen, and how errors can be prevented.

For now, prescribers need to know that e-prescriptions sent to outpatient pharmacies cannot be recalled or discontinued without calling the pharmacy directly. To address this issue, the Office of the National Coordinator for Health Information Technology (ONC) Health IT Certification Program has just published proposed certification criteria for 2015 that would require e-prescribing systems to notify the pharmacist that a previously sent prescription should be cancelled and not filled (www.ismp.org/sc?id=546). Health IT certification provides assurance to purchasers that a system meets the technology capability, functionality, and security requirements adopted by the Secretary of Health and Human Services. Thus, we can anticipate that vendors will seek to comply with these criteria when the proposed rule becomes a final rule.



Is it calcium gluconate, sterile water, or 0.9% sodium chloride? In our May 7, 2015 newsletter, we sounded a cautionary note about a potential drug selection error now continued on page 3—**SAFETY briefs** >

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ceived the incorrect dose of 5,860 mg. The patient was admitted to the hospital where he received the antidote, uridine triacetate, and was monitored.

Case of Pump Failure

This month, our 2014-2015 Safe Medication Management Fellow, Ivyruth Andreica, BSN, PharmD, coauthored an article about the management of fluorouracil overdoses during and after hospitalization.³ The authors followed a 60-year-old man admitted to the emergency department (ED) following a confirmed fluorouracil overdose, from initial exposure through posthospitalization and recovery. He had received the full dose (3,974 mg) of fluorouracil along with overfill in the container (469 mg) over 20 minutes instead of the intended 46 hours. The patient was asymptomatic upon presentation in the ED, but supportive treatment for the overdose was started immediately, and the initial dose of uridine triacetate was given 20 hours after the overdose was identified. He was discharged after a week but developed neutropenia following discharge, which required additional treatment.

Older Case Report

In our September 20, 2007 newsletter, we wrote about a 43-year-old Canadian woman who died as a result of an accidental overdose of fluorouracil that was administered over 4 hours instead of 4 days. Two nurses miscalculated the infusion rate, forgetting to divide the daily dose by 24 hours. They were also misled by the pharmacy label on the infusion, which listed the mL per day rate of infusion first, followed by the mL per hour rate. The nurses saw the “28.8 mL/24 hours” and believed their calculations for an hourly rate were correct. Multitasking, a failed independent double-check system, the failure to use a smart infusion pump, confusing choices when programming the pump, and a review screen on the pump that did not include the duration of the infusion also contributed to the event. When the patient called to report that the entire infusion had infused in 4 hours, she did not receive prompt treatment of the overdose. She visited the clinic the next day but was treated and discharged because there were no beds available in the local hospital. She was finally admitted to the hospital the following day, but she died 22 days after the overdose from hemodynamic collapse and multisystem organ failure.

SAFE PRACTICE RECOMMENDATIONS: Preventing errors with fluorouracil is clearly the goal for those who prescribe, dispense, or administer this cytotoxic drug. When errors or toxicity occur, prompt treatment of the life-threatening condition can help avoid serious and permanent harm. Consider the following recommendations to prevent or manage fluorouracil toxicities, particularly those caused by overdoses.

Preventing Errors

Prescribe clearly. Prescribers should order fluorouracil clearly in single daily doses (not course doses) with directions to infuse continuously over a specific number of days or hours (e.g., 750 mg/m²/day continuous infusion days 1 through 5).

Review chemotherapy certification processes. Review the processes by which certification is granted to prescribers, pharmacists, and nurses who order, dispense, and administer fluorouracil and other chemotherapy. Make any changes necessary to ensure that staff exhibit and maintain an appropriate level of skills, knowledge, and abilities before working independently.

Use pumps with safeguards. Smart pumps for use in ambulatory care settings are available, and their use should be encouraged to maximize safety features such

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that calcium gluconate 1 g/10 mL from Fresenius Kabi is available in plastic vials instead of the previous glass vials. Although the label appearance has not changed, the product now appears similar to vials of 10 mL sterile water for injection from Hospira. Each vial is about the same size, with a similar cap color (**Figure 1**). We had also received a report regarding similarities between the Fresenius Kabi's 10 mL vials of calcium gluconate and the company's



Figure 1. Photo shows similarity of plastic vials of sterile water (left) and calcium gluconate (right).

own 0.9% sodium chloride injection vials. However, the sodium chloride vials have a pink cap, helping to differentiate it, at least until the cap is removed.

ISMP continues to receive reports of potential mix-ups between these products, especially the calcium gluconate and sterile water vials. All three vials are well labeled, and no actual errors have been reported. But overall appearance sometimes plays a role in medication errors, especially when a clinician fails to read the full label of a partially turned vial when returning an unused item to stock or retrieving it from a labeled storage bin. A mix-up in the pharmacy or on the nursing unit could lead to an adverse outcome. We would normally advise purchasing another manufacturer's product for one product or the other, but that may not help given the persistent calcium gluconate shortage situation. One hospital pharmacist who recently reported the risk of mix-ups said he planned to switch to a 20 mL vial of sterile water. This may help differentiate the products, but staff who are accustomed to sterile water in the 10 mL

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as dose alerts, dosing and flow rate limits, and operator feedback to allow detection of pump programming errors. Conduct usability testing and a failure mode and effects analysis to evaluate pumps in current use and under consideration for purchase, to uncover risks and reduce the chance of programming errors. If possible, use only one type of ambulatory pump throughout the organization.

Provide education and validate competency. Educate staff to program and connect ambulatory infusion pumps (and elastomeric pumps that are used at your facility). This includes home care nurses who might come into an infusion center to connect the patient to the ambulatory infusion pump. If elastomeric pumps must be used, educate key clinical staff regarding their use and validate competency. Ensure initial and ongoing competency validation is maintained.

Enhance independent double checks. Promote critical thinking during the preparation and checking of all chemotherapy. Develop a structured process for conducting and documenting independent double checks after preparation and prior to administering fluorouracil (and all chemotherapy agents). Incorporate instructions related to this process into staff orientation and annual competencies. Design checklists to facilitate compliance with all the steps necessary in the checking process. Establish how verification can be accomplished if only one practitioner is on duty, or if home care nurses provide care in the oncology clinic or in the home. For example, include a review of pump data-input screens when teaching patients about their therapy to provide a final opportunity for a solo practitioner to review data input and possibly detect incorrect programming. Or an educated patient and/or family member can play a role in the verification process, particularly when the chemotherapy is initiated in the home. Minimize the need for dose calculations (other than recalculating doses for verification) whenever possible.

Standardize how key information is displayed on pharmacy labels. Ensure that the information needed to program an infusion pump (e.g., total volume, concentration, hourly rate of infusion) is prominently displayed in a standard and consistent way on pharmacy labels that sequentially matches the information that the nurse needs to enter into the infusion pump fields. Eliminate extraneous information, such as mL per 24 hours, and communicate infusion rates as an hourly rate only.

Teach patients. Patients, especially those receiving ambulatory fluorouracil infusions, should be instructed about reporting symptoms and to call with questions or concerns they may have about the infusion pump or drug delivery system. Also teach patients about the total dose they are receiving, the length of time the infusion should last, and to periodically check to make sure the volume is not infusing too quickly.

Managing Toxicity

Define treatment protocols for overdoses. Define a treatment protocol for fluorouracil overdoses and establish triage plans so that decisions can be made promptly regarding the treatment of the overdose with uridine triacetate tablets, the only antidote available. A 98% rate of full recovery and reduced symptoms of toxicity have been reported with administration of the antidote using a common treatment protocol (noted below).^{1,6} Protocols should guide the timely procurement of uridine triacetate (formerly called vistonuridine), which is supplied by Wellstat Therapeutics (Hotline 443-831-5626) for emergency use under a single-patient Investigational New Drug (IND) provision. Also, clear instructions regarding how to obtain this medication should be available in inpatient and outpatient oncology areas, the ED, and the pharmacy.

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vials may still mistakenly pick up a 10 mL vial of calcium gluconate, believing it is sterile water. Barcode scanning, increasing awareness of the risk, and storing these products far apart can help prevent errors. Fresenius Kabi is aware of the reports and has informed us of its plans to make changes to reduce vial similarities.



Seasonale or seasonal? Inaccurate or inappropriate allergies may be documented in health records when patients report “seasonal allergies.” **SEASONALE**, the brand name of an oral contraceptive containing levonorgestrel and ethinyl estradiol, has been accidentally selected in the allergy field when the intention was to document seasonal allergies. A hospital reported a persistent problem with providers selecting this choice. Their system records only actual substances (e.g., pollen, birch) to which a patient is allergic. “Seasonal” is not a choice, but staff see Seasonale listed and select it, believing they’ve found the right term. Thus, inaccurate allergy information is recorded, and the patient might be misdiagnosed with a birth control pill allergy in their medical record.

That’s exactly what happened when we first reported this error in our January 26, 2012 issue. A patient reported that she had seasonal allergies. The nurse typed ‘seasonal’ into the allergy database without realizing that the system converted it to Seasonale. Later, a medication reconciliation technician asked the patient about her allergy to Seasonale and learned that the patient did not have a uterus and had no need for the contraceptive, but she did experience seasonal allergies. In this case, no harm occurred, but one can imagine a scenario where a patient’s oral contraceptive or hormone replacement therapy is never prescribed, or is discontinued inappropriately, based on the incorrect information.

If you list Seasonale in your allergy database, remind staff about potential mix-ups with seasonal allergies, and to never select this drug unless the patient is truly allergic to the medication.

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Recognize overdoses/toxicity promptly. Staff who administer fluorouracil and/or monitor patients who receive fluorouracil should be aware of the signs and symptoms of toxicity and monitor patients closely both during and after drug administration to promptly recognize these signs. Nurses should be knowledgeable about when symptoms require an ambulatory patient to be brought in for assessment. For instance, mouth sores that develop 1-3 days after receiving fluorouracil are cause to bring the patient in for assessment, whereas those that occur more than a week after treatment are bothersome, but common, adverse effects.¹ Provide clear guidance regarding how to communicate signs of potentially life-threatening toxicity in a prompt and meaningful way to others providing care to the patient to manage it proficiently.

Provide prompt treatment. If toxicity or an overdose is identified, administer uridine triacetate 10 mg orally every 6 hours for 20 doses, starting as soon as possible (within 96 hours) after an overdose. While awaiting the arrival of the antidote, patients should be admitted to a hospital, and supportive care should be provided to reduce symptom severity (e.g., IV hydration, electrolyte replacement, treatment of diarrhea, mouth and skin care, human granulocyte colony-stimulating factor administration, continuous cardiac monitoring).

Avoid contraindicated medications. Avoid medications that might interfere with absorption of the antidote, (e.g., bismuth subsalicylate, sucralfate, cholestyramine) or reduce clearance of fluorouracil (e.g., cimetidine, metronidazole, thiazide diuretics).³ Use caution with medications that are metabolized by cytochrome P450 2C9 (e.g., phenytoin, clozapine).³

Close monitoring posthospitalization. It should also be noted that fluorouracil overdoses are difficult to treat due to the length of the drug effect. Thus, patients must be monitored closely posthospitalization for delayed adverse effects, particularly throughout the expected neutrophil nadir.³ Human granulocyte colony-stimulating factors may be required to treat myelosuppression, and antibiotics may be needed to prevent infections.

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Special Announcements

ISMP webinars

Join us on **June 24** for our **2015 Update on The Joint Commission Medication-Related Standards**. Learn about the most troublesome Medication Management Standards and National Patient Safety Goals along with successful approaches taken by healthcare organizations to accomplish the intent of these Standards. A second presenter will describe a recent Joint Commission survey at a large teaching hospital.

Join us on **July 30** for **Missed Safety Opportunities with Subcutaneous Insulin: Addressing the Often Unknown Safety Challenges with Insulin**. A 2014 ISMP survey suggests that pharmacists and nurses believe hospitalized patients are more vulnerable to errors with subcutaneous insulin than errors with any other high-alert medication. Join us as we discuss standardizing basal/bolus insulin doses, managing overlooked risks associated with prescribing, dispensing, and administering subcutaneous insulin, and challenges with patient assessment, education, and adherence.

For details, visit: www.ismp.org/sc?id=349.

Take our survey!

don't forget

ISMP is repeating a short survey to get a sense of progress with implementing the **2014-2015 Targeted Medication Safety Best Practices for Hospitals**. You can take the survey until **July 8, 2015**, by going to: www.surveymonkey.com/r/TMSBP2015. We appreciate your participation even if you have not implemented the practices!

If you would like to subscribe to this newsletter, visit: www.ismp.org/sc?id=382



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