Accidental Overdoses Involving Fluorouracil Infusions

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PROBLEM: Approved more than 50 years ago, fluorouracil was one of the first intravenous (IV) 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 250,000 Americans receive fluorouracil annually; of those, about 8,000 experience a toxic reaction, with some 1,100 patients dying each year from toxicity.2,3 Impaired clearance of the drug and medication errors are usually responsible for these adverse events.3

The literature describes dozens of fluorouracil errors,1,4 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 The Institute for Safe Medication Practices has received numerous reports of accidental overdoses with fluorouracil, including those that follow.

Report No. 1

A young patient received 4,500 mg of fluorouracil IV within two 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 two-day course of therapy over two 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 two weeks, the patient improved and was discharged home.

Report No. 2

A patient was to receive 4,000 mg of fluorouracil by IV infusion at 2 mL per hour over four days, but he accidentally received the entire four-day dose in less than one hour. The error was caused by a mix-up between an Easypump (B. Braun Medical, Inc.) 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-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 [Vistogard, Wellstat Therapeutics]).

We learned that the pump manufacturer uses color to differentiate the 19 different Easypump configurations, placing a colored 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)—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 its usual chemotherapy elastomeric pumps. As a result, it ordered the Easypump as a backup, and thus, a pump with the wrong flow rate was used to deliver the fluorouracil infusion.

Report No. 3
In this report, the patient received a fivefold overdose of fluorouracil. The recommended dose was 200 mg/m² per day as continuous infusion for five days, but the oncologist wanted this treatment to infuse for only 100.5 hours (4.2 days), not a full five 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 five 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 removed, he received uridine triacetate and reported symptoms such as flulike illness. It was monitored. In this report, the patient received a fivefold overdose of fluorouracil. The recommended dose was 200 mg/m² per day as continuous infusion for five days, but the oncologist wanted this treatment to infuse for only 100.5 hours (4.2 days), not a full five 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 five 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 removed, he received uridine triacetate and reported symptoms such as flulike illness. It was monitored.

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 per 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 as dose alerts, dosing and flow rate limits, and operator feedback to allow detection of pump programming errors. Conduct usability testing and a failure modes and effects analysis to evaluate pumps in current use and under consideration for purchase. 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). Protocols should guide the timely procurement of uridine triacetate (formerly called vistosuridine), which is supplied by Wellstat Therapeutics (Hotline 433-831-5626) for emergency use under a single-patient investigational new drug provision. Also, clear instructions regarding how to obtain

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this medication should be available in inpatient and outpatient oncology areas, the emergency department, and the pharmacy.

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 one to three 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 six 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 after hospitalization. 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.

REFERENCES

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP website (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAIL-SAFE or via email at ismpinfo@ismp.org.