

Fluorouracil Incident Root Cause Analysis: Follow-Up

In 2006, ISMP Canada was invited to provide external expertise to conduct a root cause analysis of a medication incident involving administration of a *high dose* of fluorouracil (4000 mg/m²; total dose 5250 mg) over 4 hours instead of 4 days, as intended. (The protocol also included administration of a single dose of 100 mg cisplatin.) The patient, a 43-year-old woman with advanced nasopharyngeal carcinoma, died 22 days later from the sequelae of fluorouracil toxicity, cumulative with cisplatin toxicity. The *Fluorouracil Incident Root Cause Analysis Report*ⁱ was released for shared learning in May 2007. The recommendations in the report, although directed toward safer management of high-dose fluorouracil protocols, may be relevant to the management of other chemotherapy agents, as well as other high-alert medications. This bulletin provides a brief overview of the findings and recommendations from this root cause analysis and describes some of the local and national efforts now underway to implement the recommendations for enhancing patient safety.

Root Cause Analysis

Root cause analysis is a structured process for completing a comprehensive system-based review of critical incidents to determine what happened, why it happened, and what can be done to reduce the likelihood of recurrence.ⁱⁱ Root cause analysis of medication incidents identifies hazards, issues, contributing factors, and underlying causes. The resulting information is used to develop safeguards to prevent similar adverse events or to mitigate harm to patients if incidents do occur again. Providing assistance with such analyses is one of ISMP Canada's defined roles in the Canadian Medication Incident Reporting and Prevention System (CMIRPS).

Brief Description of Identified Causes

The defined event for this analysis was the death of a patient due to the sequelae of fluorouracil toxicity, cumulative with cisplatin toxicity. This event was not the result of a single "root cause". Rather, a combination of actions and conditions, each of which on its own would not have caused the event, together were causal. Three primary causal chains were identified:

1. Fluorouracil overdose

The patient received fluorouracil 5250 mg over 4 hours rather than 4 days. Seven causal chains led to the infusion rate being entered as 28.8 mL/h instead of 1.2 mL/h: miscalculation, opportunity for false confirmation on the pharmacy label, information required to program the pump not being part of the medication administration record (MAR), failure of the double-check process, complex workload and multitasking, lack of feedback from the pump, and limited knowledge of the hazard.

2. Design of the chemotherapy protocol

The amount of fluorouracil contained in the infusion bag (4 days' supply), as per the treatment protocol for nasopharyngeal carcinoma, was sufficient to result in overdose. Cisplatin was administered as a single dose of 100 mg, also according to the protocol. (Some protocols use cisplatin 20 mg/m² daily for 5 days instead of a single dose.ⁱⁱⁱ)

3. Inability to mitigate harm from fluorouracil and cisplatin

The absence of an antidote or defined treatment plan for fluorouracil overdose increased the likelihood that a significant overdose would cause harm. In addition, the absence of a defined treatment protocol to reverse cisplatin toxicity increased the potential for cumulative toxicity with fluorouracil.

Through a process of cause-and-effect diagramming and analysis, each of these causal chains was further expanded to allow a more detailed understanding of the underlying causes of the patient's death. These are summarized below in order of priority:

1. Information needed to guide administration was not included in the medication order.
2. Programming of the infusion pump relied on complex calculations at the bedside (specifically dose [mg] divided by days, divided by hours, divided by concentration [mg/mL] to determine the infusion rate [mL/h])
3. The pharmacy label presented opportunities for false confirmation:
 - a. Unnecessary information was present (e.g., mL/24 h).
 - b. Label design did not incorporate human factors engineering principles (e.g., prominence of critical information).
4. Critical information that nurses needed to administer medications correctly was not mapped between the medication order, the MAR, the pharmacy label, and the pump.
5. The infusion pump did not have programming safeguards.
6. A process to ensure truly independent double checks was lacking.
7. Standardized embedded structures for checking functions in nursing practice were lacking.
8. Mental approximation was not used to validate calculations.
9. The patient teaching process did not include review of pump data input, which resulted in a missed opportunity

for the practitioner to detect the incorrect data that had been entered into the pump.

10. Human factors design flaws in the infusion pump increased the complexity of programming and the associated cognitive load.
11. Variations in clinical practice between the 2 tertiary cancer treatment centres within the provincial cancer board made it difficult to build detailed common order sets for the shared computerized prescriber order entry (CPOE) and pharmacy information systems.
12. Limited integration and standardization between the 2 tertiary cancer treatment centres within the provincial cancer board prevented optimization of the shared CPOE and pharmacy information systems.
13. Information about previous incidents with high-dose fluorouracil was difficult to find or not available
14. There was limited knowledge about the culture of “high-reliability organizations” and the application of human factors engineering design principles to enhance the safety of health care environments.
15. The design of the treatment protocol (i.e., 4 days of high-dose fluorouracil prepared and administered in one infusion bag), combined with a single high dose of cisplatin, increased the likelihood that programming the infusion pump with incorrect data would result in the patient’s death.
16. Absence of a defined treatment protocol for fluorouracil overdose.

In addition to these 16 root causes, the analysis also identified 5 important associated findings:

1. Absence of a system to triage medication incidents and assess the need for intervention.
2. There was a low index of suspicion, because relevant learning from previous incidents with high-dose fluorouracil is difficult to find or not available.
3. A poison information centre was not considered as an additional information resource in the initial management of the overdose.
4. The expected course and plan of care were not documented in the patient’s health record, which led to variable perceptions of the level of clinical monitoring and intervention needed.
5. Continuity of care between the tertiary cancer treatment centre and the tertiary acute care facility was not optimally supported by communication and information systems.

The following recommendations, directed at various aspects of the medication-use system, are suggested for consideration, in order to reduce the potential for recurrence of this or a similar event.

Cancer Treatment Centres and Hospitals

Medication Orders and Administration Protocols

1. Include critical information required for medication administration as part of standardized order sets in manual

and electronic orders. For example, if optimal programming of an infusion pump requires data input of “total volume” and “rate of infusion”, these data should be available in the medication order.

2. Standardize administration procedures for high-dose fluorouracil infusion protocols; include this information and the critical calculations required as part of electronic order sets and/or preprinted manual orders.
3. Standardize communication of orders for infusion of medication to refer to rates as “millilitres per hour” (mL/h) instead of “millilitres per 24 hours” (mL/24 h).
4. Develop a mechanism to ensure adequate consultation with multiple front-line staff regarding medication use.

Medication Labels, MARs, and Other Communications

5. Remove “mL/24 h” rate information from medication labels, MARs, and other communications about medications to be administered by infusion.
6. Have a multidisciplinary team review pharmacy-generated medication labels in the context of medication administration requirements. Consider human factors design principles to improve readability.^{iv v}
7. Design medication orders, MARs, and medication labels to ensure that the critical information required to program infusion pumps for administering medications is available and provided in a logical sequence, with consistent terminology.

Ambulatory Infusion Pumps

8. Use pumps with safeguards such as controlled-rate delivery (e.g., elastomeric pumps or pumps with preset maximum rates for mL/h) until such time as “smart pump” technology is available for ambulatory infusion pumps.
9. Review confusing aspects of the programming sequence for the infusion pump with all hospital staff who use the pump and during training of new staff.
10. Conduct usability testing with a multidisciplinary team of 4 to 6 users to evaluate pumps in current use and under consideration for purchase.

Double-Check Processes

11. Incorporate checklists and calculations into medication order forms and MARs to embed specific checking procedures where required.
12. Develop a structured process for conducting and documenting independent double checks, and incorporate training related to this process into staff orientation and recertification programs.
13. Include information about mental estimation as part of training and orientation about checking processes.
14. Include a review of pump data-input screens when teaching patients about infusion pumps, in order to provide a final opportunity for practitioners to review data input and possibly detect incorrect programming.

Computer Information Systems

15. Standardize preparation and administration processes for chemotherapy to ensure the consistency needed to build detailed order sets for CPOE and pharmacy information systems.
16. Develop standardized order sets for CPOE and pharmacy information systems that reflect the administration information needed by nurses.
17. Enhance the institutional information system to provide a direct interface between the CPOE and pharmacy information systems.

Management of Medication Incidents

18. Develop a triage process for medication incidents to ensure timely medical review of incidents with a high potential to cause patient harm, regardless of the severity rating on the incident report.
19. Create a multidisciplinary rapid response team that can be quickly convened to provide assistance in managing medication incidents with potential for serious harm.
20. Develop a protocol for dealing with potentially serious medication incidents that includes the need to consider contacting the regional poison information centre.
21. In the absence of a defined treatment protocol for fluorouracil overdose, include provision of aggressive supportive care in the immediate treatment plans for such overdoses (e.g., IV hydration and forced diuresis, timely administration of hematopoietic growth factors and prophylactic antibiotics).
22. In the setting of a high-risk drug overdose, ensure that a detailed consultation note from a medical oncologist (or attending physician, in the case of a non-chemotherapy drug) is added to the patient's health record and communicated through direct contact with front-line medical and nursing personnel who are involved in the patient's care.

Organizational Culture and Communication

23. Improve awareness of the attributes of high-reliability organizations through ongoing education efforts and implementation of high-visibility safety-promotion activities.
24. Enhance communication and information systems for transitions of care between transferring and receiving centres.

In addition to recommendations for cancer treatment centres and hospitals, the following recommendations will require assistance from regulatory authorities, patient safety organizations (in Canada and internationally), manufacturers of ambulatory infusion pumps, researchers, and oncology journal editors.

Patient Safety Agencies

1. Disseminate an international warning about the use of "millilitres per 24 hour" (mL/24h) rates and the use and/or manufacture of infusion pumps that require "millilitres per 24 hour" (mL/24 h) rates.

2. Develop a worldwide taxonomy, minimum data set, and transparent database to allow the various existing medication incident databases to submit data, collected at the local level, for shared international learning.
3. Develop a Medication Safety Self-Assessment® program specific to systemic antineoplastic therapy to assist oncology practitioners in identifying areas of risk particular to this specialized field.

Regulatory Authorities

4. Develop international standards for infusion pump terminology and functionality.

Manufacturers of Infusion Pumps

5. Design and manufacture ambulatory infusion pumps with added safeguards (e.g., built-in software libraries) for chemotherapy drugs.
6. Enhance the functionality of ambulatory infusion pumps to include calculation and display of infusion duration on the basis of programmed values.
7. Enhance the features of ambulatory infusion pumps to include an information display screen that summarizes critical information.

Researchers

8. Establish the development of treatment protocols for cases of inadvertent overdose of antineoplastic drugs as a patient safety research priority.
9. Research delivery options for the administration of cisplatin and fluorouracil within the chemotherapy protocols for head and neck cancer, considering the potential for harm in the event of an infusion pump-related medication incident.
10. Develop consensus guidelines as to what constitutes an "overdose" or "infusional variance". For example, an overdose might be defined as a dose that is 10% greater than the correctly calculated dose and an infusional variance might be defined as an infusion administered over an interval that is 25% different from the intended time.
11. Conduct and publish studies on the incorporation of independent double checks into nursing practice routines.

Oncology Journal Editors

12. Invite submissions of case reports of medication incidents with fluorouracil to create a body of knowledge related to fluorouracil overdose.

Update on Follow-Up Actions

Local level: A pharmacist has been selected to lead implementation of the recommendations throughout the cancer treatment facilities in the province where this incident occurred. Priority has been given to organizational decision-making related to the use of continuous infusion pumps in the ambulatory setting. The provincial Pharmacy & Therapeutics Committee reviewed the ambulatory infusion pumps that are

currently available and considered the hierarchy of effectiveness of various safety features. A decision was made to switch to elastomeric pumps for all fluorouracil protocols until smart pump technology for electronic ambulatory infusion pumps becomes available. Other drugs administered as ambulatory continuous infusions are being evaluated to determine if they are compatible with elastomeric pump delivery. If continued use of electronic pumps is required, additional safety measures will be implemented. The provincial cancer treatment agency will eliminate use of any pumps that require programming in millilitres per 24 hours. In addition, future participation in clinical trials will be contingent on the ability to utilize the pumps that are in standard use in these centres. The “mL/24 h” information on the pharmacy label was removed immediately following the incident. Further recommendations regarding incorporation of

human factors engineering principles into the design of pharmacy labels will be reviewed over the coming months.

National level: It was clear from the analysis findings that a similar incident could happen in other health care organizations and that system failures identified in this case are likely to exist in cancer treatment centres across Canada and in other countries. A Systemic Therapy Working Group on Critical Occurrences has been formed through the Canadian Association of Provincial Cancer Agencies, with representation from additional key stakeholders. The aim of this working group is to review the recommendations from this RCA for potential application on a national scale and to develop consensus and a common approach to implementing safety enhancements.

For complete details, readers are encouraged to review the full report, available at:

<http://www.cancerboard.ab.ca/NR/rdonlyres/2FB61BC4-70CA-4E58-BDE1-1E54797BA47D/0/FluorouracilIncidentMay2007.pdf>

ⁱ Fluorouracil incident root cause analysis [Internet]. Toronto (ON): Institute for Safe Medication Practices Canada; 2007 May 22 [cited 2007 Jul 17]. Available at: <http://www.cancerboard.ab.ca/NR/rdonlyres/2FB61BC4-70CA-4E58-BDE1-1E54797BA47D/0/FluorouracilIncidentMay2007.pdf>.

ⁱⁱ Canadian Patient Safety Institute; ISMP Canada; Saskatchewan Health. *Canadian root cause analysis framework* [Internet]. Edmonton (AB): Canadian Patient Safety Institute; 2006 [cited 2007 Jul 31]. Available at: http://www.patientsafetyinstitute.ca/uploadedFiles/Resources/RCA_March06.pdf.

ⁱⁱⁱ Cisplatin monograph [Internet]. In: *Cancer Care Ontario formulary*. Toronto (ON): Cancer Care Ontario; revised 2006/2007 [cited 2007 Jul 31]. Available at: <http://www.cancercare.on.ca/pdfdrugs/cisplati.pdf>.

^{iv} Designing labels with the end-user in mind. *ISMP Can Saf Bull* 2002;2(9):1-2 [cited 2007 Aug 7]. Available at: <http://www.ismp-canada.org/download/ISMPCSB2002-09Labels.pdf>.

^v Principles of designing a medication label for injectable syringes for patient specific, inpatient use [Internet]. Huntingdon Valley (PA): Institute for Safe Medication Practices; 2007 [cited 2007 Jul 23]. Available at: <http://www.ismp.org/Tools/guidelines/labelFormats/injectionSyringe.asp>.

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ISMP Canada is a national voluntary medication incident and ‘near miss’ reporting program founded for the purpose of sharing the learning experiences from medication errors. Implementation of preventative strategies and system safeguards to decrease the risk for error-induced injury and thereby promote medication safety in healthcare is our collaborative goal.

Medication Incidents (including near misses) can be reported to ISMP Canada:

- (i) through the website http://www.ismp-canada.org/err_report.htm or
- (ii) by phone: 416-733-3131 or toll free: 1-866-544-7672.

ISMP Canada can also be contacted by e-mail: cmirps@ismp-canada.org. ISMP Canada guarantees confidentiality and security of information received, and respects the wishes of the reporter as to the level of detail to be included in publications.

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