An Opioid-Related Death in a Small Community Hospital

Pain management is a complex process that can involve a number of pharmacologic treatment modalities, including traditional pain medications (e.g., non-opioids and opioids) and adjunctive pharmacotherapy (e.g., anticonvulsants, antidepressants). Choosing an appropriate starting dose for an opioid, titrating opioid doses, using more than one opioid, and converting from one opioid to another are all elements of pain management wherein errors can lead to significant harm. This bulletin shares findings and recommendations from an ISMP Canada review of an unexpected death that occurred after admission to a small community hospital for management of acute pain. The system vulnerabilities identified during this analysis likely exist in other facilities, and all those affected by this case sincerely hope that the learning shared here will lead to system improvements in hospitals across Canada.

Incident Description

A woman was admitted to hospital for management of pain. Five years earlier, she had undergone back surgery for chronic pain, and her condition was reported to have improved until an injury occurred about 2 months before the hospital admission. According to available prescription records, opioid medication had been prescribed for previous injuries, and it was believed that the patient was taking about 4 tablets of an oxycodone–acetaminophen combination tablet daily before this most recent injury. The combination tablet had been taken more frequently subsequent to the injury, and hydromorphone in both immediate-release (IR) and controlled-release (CR) formulations had also been trialled to address the patient’s uncontrolled pain.

The most recent prescriptions, written and dispensed 1 week before the admission, were for CR oxycodone and IR hydromorphone. However, at the time of admission, the patient described use of CR oxycodone only. Opioid usage for the week before admission is detailed in Figure 1. Other medications being taken just before admission included metformin, glyburide, irbesartan, and amitriptyline. After admission, the patient continued taking CR oxycodone, and several other pain medications (including fentanyl patch) were initiated, as shown in Figure 2.

On the evening of Day 14, the fentanyl dose was increased. Overnight, the patient did not sleep well and was awake for part of the night. On the morning of Day 15, she was left to sleep and was not awakened for breakfast or for usual medication administration. She was found with vital signs absent at about 11 am. Resuscitative efforts were unsuccessful.

The cause of death was determined to be “mixed drug toxicity” on the basis of autopsy and toxicology findings. This determination of mixed drug toxicity takes into consideration the toxicological findings and the combined effects of several of the medications detected post mortem.
Figure 1. Timeline of known opioid use in the week leading up to hospital admission (according to available prescription records).

<table>
<thead>
<tr>
<th>Oxycodone CR 20 mg, 2 times daily, prescribed and taken (1 week before admission)</th>
<th>Oxycodone CR 20 mg, 4 times daily, taken (2 days before admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital admission</td>
</tr>
<tr>
<td>Short-acting hydromorphone 2 mg, 2 to 4 times daily as needed (1 week before admission - use unknown)</td>
<td></td>
</tr>
</tbody>
</table>

CR = controlled-release

Figure 2. Timeline of use of opioids and other regularly scheduled adjunct medications during the hospital admission

<table>
<thead>
<tr>
<th>Morphine 2−5 mg IV/SC q1h prn and oxycodone CR* prescribed (on admission – Day 1)</th>
<th>Cyclobenzaprine changed from as needed to q6h routine use (Day 6)</th>
<th>Hydromorphone 2−4 mg orally q2h as needed and gabapentin 100 mg 3 times daily (to be titrated upward), prescribed and started (Day 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Day 2) Fentanyl 75 mcg/h patch, prescribed and started</td>
<td></td>
<td>(Day 12) Oxycodone CR discontinued (Day 14) Fentanyl increased to 150 mcg/h and gabapentin increased to 200 mg 3 times daily</td>
</tr>
</tbody>
</table>

*the daily dose of CR oxycodone varied from 40 to 80 mg until it was discontinued on Day 12
IV = intravenously; SC = subcutaneously

ISMP Canada’s Findings

An interdisciplinary review identified several system-based vulnerabilities and factors potentially contributing to the patient’s death. Key opportunities to prevent future deaths were thought to be related to the overall approach to pain management, including opioid selection, dose conversion and titration, and monitoring of symptoms and adverse effects. These opportunities, along with other selected factors, are highlighted in the current bulletin.

Approach to Pain Management

Opioid Selection

The hospital did not have a standardized protocol for pain management, and the patient’s pain was being managed with several different opioid analgesics and a number of adjunctive agents (amitriptyline, cyclobenzaprine, gabapentin, and naproxen). Use of more than one opioid at the same time increases the complexity of dosing and titration and complicates conversion from one opioid to another.
Of particular concern was the use of a fentanyl patch for a patient whose analgesic needs had not been fully determined. Other concerns included the initial and titration doses of fentanyl, concomitant use of more than one long-acting opioid, absence of orders to address breakthrough or variable pain, and use of adjunctive agents with sedative properties without a corresponding reduction in opioid dosage.

**Opioid Dose Conversion and Titration**

Initial and titration doses (based on generally accepted conversion factors) used in this case were higher than doses recommended in available protocols. Calculation of “morphine equivalents” provides a way to compare the relative potency of other opioids with that of morphine. This calculation is particularly important for converting from one opioid to another and for evaluating the total opioid dose when multiple opioids are being used concurrently. Research has shown that doses of opioids exceeding the equivalent of 200 mg of oral morphine daily are associated with an increased risk of opioid-related death. This research has also shown that calculation of morphine equivalents can help the practitioner to assess whether a patient’s overall opioid dose is reaching levels that might cause concern.

On the basis of available prescription records and information provided by the patient at the time of admission, the reviewers estimated that the 24-hour oral morphine equivalent on the day before admission was 120 mg. By Day 3 and for the remainder of the admission, the daily morphine equivalent was calculated to be well over 300 mg, and rose to over 400 mg with the increase in the fentanyl dose on Day 14. On the day of death (Day 15), it was estimated that the patient would have received the equivalent of 540 mg/day of morphine, if the full dose of fentanyl had been given as prescribed. However, this is a conservative estimate, as one manufacturer’s conversion guideline indicates that a 75 mcg/h fentanyl patch is equivalent to a range of 270 to 314 mg oral morphine.

Despite the high doses of opioids received during her hospital stay, the patient continued to complain of pain. There is a common misperception among health care professionals that patients who continue to experience pain, despite receiving pain medications, are not at risk of opioid toxicity. For such patients, opioids can indeed be titrated to very high doses, but the titration must be done slowly and carefully to avoid toxic effects. The total opioid dose (in terms of estimated morphine equivalents) placed this patient at high risk of opioid-related toxicity and death.

Changing from one opioid to another and selecting an appropriate dose of the next opioid is an inexact science and the selection of a particular conversion factor can have a profound effect on the suggested dose of the intended opioid. For example, hydromorphone is considered to be 4 to 8 times more potent than morphine, so 10 mg of hydromorphone is equivalent to a morphine dose of 40 mg to 80 mg. Depending upon the conversion factor used in a particular guideline, this difference can also have a profound effect on the dosing of other opioids, such as fentanyl patches. Incomplete cross-tolerance, whereby a patient may be more sensitive to the same relative potency of the new opioid than the previous agent, must also be taken into account. A number of guidelines and web-based applications are available to support calculation of conversions from one opioid to another; however, a wide range of conversion factors are used in these guidelines and programs. Having another practitioner, such as a pharmacist, independently perform the conversion calculations can be a valuable safeguard.

**Monitoring of Symptoms and Adverse Effects**

Formal and consistent evidence of pain and symptom assessment, systematic determination of the effectiveness of analgesics, and routine evaluation for opioid toxicity were not apparent in the nursing or medical notes available for this patient. Vital signs were documented at most once daily, and no vital signs were documented on 5 separate days during the patient’s hospital stay. On those days when vital signs were obtained, the documented heart rate was above the upper limit of the normal range. Patient monitoring and assessment were compromised by approved leaves of absence during the admission, whereby the patient was absent from the hospital for most of the day on nearly every day of the admission.

During her hospitalization, the patient expressed concern about how her medication therapy made her
feel to the care team and to her family and friends. She reported feeling “wobbly”, “unsteady”, “groggy”, and “whacked out”. Despite these voiced concerns, staff members noted that the patient appeared to function fairly well, both physically and cognitively. The medical record included few notes related to the symptoms of toxicity. Where symptoms potentially attributable to medication toxicity were documented (e.g., one instance of noticeable unsteadiness and another instance of the patient being found slumped over in her chair), there did not appear to have been any follow-up with the attending physician. An impending opioid overdose may be difficult to detect because patients may appear to be alert when engaged, despite exhibiting signs of toxicity. These patients are at risk for succumbing to the overdose when left unmonitored.

Other Factors

Resuscitation Process

The health record indicated that when the patient was found without vital signs, it was presumed, because of her medical history and risk factors that a cardiac event had occurred. The opioid reversal agent naloxone was not administered during resuscitation efforts.

Organizational Factors

The death occurred in a small hospital in a remote community. Access to advanced diagnostic modalities and specialist care is often limited in such communities, and these factors are difficult to mitigate. In this case, access to a neurologist or pain specialist via remote consultation could have been beneficial.

At the time of this incident, there was no process in place for routine review by a pharmacist of inpatient medication orders at this hospital, a gap that has now been addressed. The importance of independent review of medication orders was highlighted in early patient safety work, which showed that nearly 40% of medication errors occur at the prescribing stage, and of these, nearly half are intercepted through review by nurses and pharmacists. In the community where this patient lived, a pharmacist was not available, which meant that physicians both prescribed and dispensed medications without independent review by a second practitioner.

In addition, the patient was a healthcare provider in the community, which may have influenced decision-making on issuing leaves of absence from the hospital.

Recommendations

A number of recommendations were offered for consideration in this case. Those recommendations thought to be generally applicable to all acute care hospitals are presented here.

Pain Management

• Develop or adopt predefined order sets and protocols for pain management. Ensure that order sets include guidance on opioid selection, recommended initial doses (with consideration of patient risk factors), guidance for dose titration, specific monitoring requirements, and triggers for intervention. Protocols should specifically state that the transdermal fentanyl patch should not be used for management of acute or acute-on-chronic pain.

• Ensure that all medication orders are reviewed by a pharmacist in a timely manner, with particular attention to orders for high-alert medications such as opioids. The review of opioid orders should include a review of opioid tolerance and morphine equivalents.

• Consider consulting an experienced opioid prescriber (e.g., acute pain service) if the patient’s daily opioid needs are greater than the equivalent of 80 to 120 mg of oral morphine, especially in cases where the patient’s pain and function have not improved.

• Undertake a detailed assessment of all processes associated with the management of opioids, including prescribing, order processing, dispensing, administration, and monitoring. Use the results of the assessment to identify and address vulnerabilities in opioid management.

• Develop clear policies and processes for management of pain medications required during a patient’s leave of absence in the course of an admission. Existing policies related to the criteria for granting leaves of absence should be reviewed to ensure appropriate consideration to the need for
patient monitoring and establishment of a standard period for a leave of absence, when granted.
• Provide ongoing education for all staff about the signs and symptoms of opioid overdose.
• Consideration should always be given to non-pharmacologic treatment options to manage pain.

**Patient Monitoring**

• Establish clear expectations for assessment of vital signs and their documentation in the health record for patients who are receiving opioids. When developing protocols for assessment and monitoring, consider the requirements for the initial period of opioid therapy, the period after a dose increase, and when concomitant medications that may depress respiration are added.
• Establish clear processes for assessment and documentation of pain level and the patient’s response to any analgesics administered. Assessment and documentation processes should establish expectations for all members of the care team.
• Provide patients and family members with information about the signs and symptoms of opioid toxicity and when to seek medical attention. An example of a patient handout developed by ISMP Canada can be found at http://www.ismp-canada.org/download/HYDROMORPHONE/ISMPCanada_OpioidInformationForPatientsAndFamilies.pdf, and a video is available from: http://youtu.be/SDMz41qnpPk.

**Resuscitation**

• Develop medical directives and protocols for the use of naloxone to ensure appropriate and timely management of opioid overdose when a need for intervention is identified.
• Ensure that naloxone administration is considered in resuscitation protocols.

**Product Documentation (for Manufacturers)**

• Revise monographs and conversion tables for fentanyl patches to indicate that these tables are for initial dose conversion only and emphasize that subsequent titration doses should never exceed 25 mcg/h.

**Conclusion**

The use of opioids to manage pain is a complex process. Previous ISMP Canada Safety Bulletins have highlighted important aspects of numerous harmful incidents associated with opioids, in particular underappreciation of the potency of hydromorphone and fentanyl.\(^8,9\) It is challenging to balance the desired outcomes of a medication regimen comprising several drug classes with mitigation of the adverse effects and potential interactions that can arise when medications with overlapping toxicities are combined. The concurrent use of more than one opioid further increases the complexity of initial dosing and dose titration. In addition, conversion calculations can be cumbersome and are prone to error. The importance of independent review of dose-conversion calculations, as can be accomplished through timely review of medication orders by a pharmacist, cannot be overstated.

The case presented here illustrates the importance of a clear care plan and a stepwise approach to managing pain that considers initial opioid selection, dose conversion and titration, monitoring parameters, and triggers for intervention, with appropriate interdisciplinary and consultative support. Readers are encouraged to use this bulletin to support review of internal processes associated with opioids in their own practice settings to avoid similar tragic events.

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References

November 2014 - Newsletter:

Know When to Stop Your Medicine!

Consumers can play a key role in making sure they take their medication for the correct length of time and no longer.

A report received recently by SafeMedicationUse.ca highlights the challenges of keeping track of when medications should be stopped. After hip surgery, a consumer was treated with an anticoagulant for 30 days as prescribed, to prevent blood clots. However, upon transfer to a nursing home 2 months after finishing the course of treatment, the anticoagulant was inadvertently restarted and continued for an additional 5 months. A family member discovered that the consumer was taking the anticoagulant again, even though this medication was supposed to have been stopped 7 months earlier. The family member informed the consumer’s doctor, who made sure that the anticoagulant was stopped.

The SafeMedicationUse.ca newsletter reminds consumers that they should know when to stop taking medicines that are intended only for a specific length of time. It also reminds consumers to keep a list of all the medicines they are taking and how to use them.

When prescribing or dispensing a medicine, practitioners can support consumers by reinforcing the reason why the medicine is needed and for how long it should be taken. In addition, when instructing a consumer to stop taking a medicine, practitioners are encouraged to inform the consumer’s pharmacy and other relevant healthcare providers. Practitioners should also update consumers’ records to ensure that discontinued medicines are removed from lists of active treatments.

Additional information for consumers and practitioners can be found at: www.safemedicationuse.ca/newsletter/newsletter_StoppingYourMedicine.html
Revise monographs and conversion tables for naloxone administration. Ensure that naloxone administration is considered in emergency situations. Establish clear processes for assessment and documentation of opioid use. Provide ongoing education for all staff about the management of acute pain. The system vulnerabilities associated with the management of opioids, including the use of opioids to manage pain, highlight important aspects of numerous harmful outcomes of a medication regimen comprising several opioids. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

The cause of death was determined to be "mixed drug toxicity." According to the toxicological analysis, the patient's last dose of fentanyl had been given as prescribed. However, this is a conservative estimate, as one dose of fentanyl had been given as prescribed. The calculated total fentanyl dose was well over 300 mg, and rose to over 300 mg in the days following.

The patient was being treated with a combination tablet of hydromorphone and fentanyl, which was taken more than once a day before the most recent event. The patient had undergone surgery for chronic pain, and her condition was assessed as increased. Overnight, the patient did not sleep well and was awake for part of the night. On the morning of admission, the patient had a heart attack, and the patient was found slumped. The health record indicated that when the patient was found without vital signs, it was presumed, because the patient was absent from the hospital for approved leaves of absence during the admission. On those days when vital signs were documented, they were documented at most once daily, and no vital signs were monitored. The patient was known to be at risk for opioid toxicity. For such patients, calculation of morphine equivalents can help the practitioner to ensure that the prescribed dose is appropriate.

Discharge was planned for the patient, and the patient had a medical history of a heart attack. The patient was on multiple medications, including fentanyl, hydromorphone, and morphine. The patient was taking fentanyl patches to indicate that these tables are for patients on opioids. The patient was taking multiple opioids, and the patient's hospital stay was the focus of the investigation. On those days when vital signs were documented, they were documented at most once daily, and no vital signs were monitored. The patient was known to be at risk for opioid toxicity. For such patients, calculation of morphine equivalents can help the practitioner to ensure that the prescribed dose is appropriate.

The patient was taking a combination of hydromorphone and fentanyl. The concurrent use of more than one opioid further increases the complexity of initial dose conversion and titration, monitoring parameters, and the period after a dose change. If the patient was at risk of opioid toxicity, the patient's opioid therapy should be monitored for the presence of opioid toxicity.

When left unmonitored, patients are at risk for succumbing to the overdose. It was determined that the patient was taking multiple opioids, and the patient's hospital stay was the focus of the investigation. On those days when vital signs were documented, they were documented at most once daily, and no vital signs were monitored. The patient was known to be at risk for opioid toxicity. For such patients, calculation of morphine equivalents can help the practitioner to ensure that the prescribed dose is appropriate.

Despite the high doses of opioids received during her hospital stay, the patient's condition was assessed as increased. On the day of death, the patient was taken to the emergency department, where she was found slumped. The health record indicated that when the patient was found without vital signs, it was presumed, because the patient was absent from the hospital for approved leaves of absence during the admission. On those days when vital signs were documented, they were documented at most once daily, and no vital signs were monitored. The patient was known to be at risk for opioid toxicity. For such patients, calculation of morphine equivalents can help the practitioner to ensure that the prescribed dose is appropriate.

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