

# Safety Issues with Fentanyl Patches Require Pharmaceutical Care

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Contributions to this column are prepared by the Institute for Safe Medication Practices Canada (ISMP Canada), a key partner in the Canadian Medication Incident and Prevention System, and include, with permission, material from the *ISMP Canada Safety Bulletin*. From time to time, ISMP Canada invites others to share learning based on local initiatives.

## INTRODUCTION

In September 2007, the media reported that the chief coroner for Ontario had launched an investigation into 3 patient deaths that appeared to be associated with the use of fentanyl patches.<sup>1</sup> The same report noted that “at least 3 more deaths in British Columbia have been linked to the same drug”. A search (on November 26, 2007) of the medication incident database maintained by the Institute for Safe Medication Practices Canada (ISMP Canada) identified 163 reports of incidents involving fentanyl patches, 14 of which had resulted in patient harm, including 1 death. ISMP Canada and its US counterpart, the Institute for Safe Medication Practices (ISMP), have described incidents related to the use of fentanyl patches in several bulletins and have provided recommendations to enhance the safe use of these products.<sup>2,5</sup> Manufacturers, Health Canada,<sup>6,7</sup> and the US Food and Drug Administration<sup>8</sup> have issued advisories and warnings about the use of fentanyl patches. ISMP recently commented that “despite warnings . . . fentanyl transdermal patches continue to be prescribed inappropriately to treat acute pain in opiate-naïve patients.”<sup>4</sup> The current article contains excerpts (used with permission) from 2 ISMP Canada bulletins describing safety issues related to fentanyl,<sup>2,3</sup> including key findings that emphasize the important role that pharmacists can play in reducing the likelihood of harm with this potent analgesic dosage form.

## CASES

The first case was described as follows by ISMP Canada<sup>2</sup>:

An adult patient with a history of chronic obstructive pulmonary disease (COPD) presented to an emergency department for management of severe back and leg pain. The patient had been receiving acetaminophen with codeine on an as-needed basis (to a maximum of 480 mg codeine per day) and had received a prescription for oral hydromorphone 2-4 mg every four hours as needed the day before from the family physician. In the emergency department, the patient was treated with intravenous ketorolac with effect, and a fentanyl patch was applied. The patient was also instructed to continue taking the previously prescribed pain medications as needed. Three days later, the patient was experiencing severe pain and returned to the family physician, who increased the fentanyl patch dose from 75 mcg/hour to 125 mcg/hour. The prescription for the new patch also included instructions for the patient to continue taking the oral hydromorphone as needed for pain. The patient returned to see the family physician the next day, reporting that the pain had improved. That evening, the patient appeared confused. The following morning, the patient was found unresponsive. Although emergency services were called, resuscitation measures were unsuccessful and the patient died.

ISMP Canada did not receive the information necessary to conduct an in-depth root cause analysis, but the following factors were identified as possibly contributing to this sentinel event:



- significant increase of opioid dose within a short time frame
- complexity of titrating fentanyl patch doses
- lack of awareness on the part of the patient and family members about the potential side effects of opioid use that would require immediate medical attention
- presence of underlying COPD

Three additional cases were reported by ISMP Canada.<sup>3</sup>

A patient was found to have new patches on their [sic] right upper arm, and old patches still on the left arm. The patient was responsive, but sluggish, with pinpoint pupils. . . .

Patient was found with a 25 microgram patch which had not been removed before an opioid infusion was started. The patient had two patches of 25 micrograms applied, and the nurse had removed only one before starting the infusion.

Patch not applied on due date and the omission was noted one day later. The patient experienced pain and required morphine.

An aggregate analysis by ISMP Canada of incidents with fentanyl patches has identified a number of contributing factors and recurring themes<sup>3</sup>:

- lack of knowledge or awareness of indications and criteria for use
- lack of knowledge of pharmacokinetics (in particular, the effects of a fentanyl patch can continue for 24 h or more after removal, through the effect of the subcutaneous depot of fentanyl)
- lack of understanding among practitioners, patients and residents, and family members that this noninvasive route of fentanyl administration is highly potent, requiring close monitoring of effects
- lack of clear communication among multiple caregivers regarding date, time, and location of application of a patch, and date and time when the next patch, is due to be applied
- use of fentanyl patches in combination with other opioid analgesics, central nervous system depressants (e.g., benzodiazepines and sedating antihistamines), or drugs that affect the metabolism of fentanyl (e.g., CYP 3A4 inhibitors that increase or prolong the effect of fentanyl [e.g., erythromycin, diltiazem, clarithromycin, ketoconazole])
- use of doses requiring multiple patches of various strengths to be administered
- application of a heat source to the patch (e.g., heating pad, hot packs), resulting in increased release and absorption of drug because of increased skin permeability; fever may also be a factor
- inadvertent contact with the patch through lack of child-resistant packaging, failure to ensure secure storage alternatives, patches falling off, and unsafe disposal of patches

- prescription of smaller doses (or smaller dose increments) than are available from the manufacturer, which can lead to inappropriate manipulation of a patch, compromising both its integrity and the sustained release of fentanyl

## PHARMACEUTICAL CARE OPPORTUNITIES

Analysis of incidents with fentanyl patches reveals opportunities for pharmacists in both hospital and community or ambulatory settings to ensure the safe use of this dosage form.

### Review of Medication Profile

Review by a pharmacist of the medication profile for any patient who has received a new fentanyl patch prescription or a dose change is a fundamental step in assessing whether the criteria for initiating and continuing this form of therapy are met. This review should include verifying that the patient is sufficiently tolerant of opioids for the dose that has been prescribed. (For example, for a fentanyl patch of 25 mcg/hour, the patient should have been receiving the equivalent of at least 60 mg of oral morphine per day for an extended period.<sup>9</sup>) Implementation of computerized alerts in pharmacy information systems may be helpful to flag situations that require extra attention, such as a dose increase of more than 25 mcg/hour or a dose increase prescribed within 6 days of starting a particular dose. Orders for fentanyl patch interpreted as 125 mcg/hour should be reviewed carefully, as there have been incidents involving orders for 12.5 mcg/hour in which the decimal marker has been overlooked.<sup>4</sup>

There may also be an opportunity to suggest adjunctive treatments (e.g., nonsteroidal anti-inflammatory agents) to decrease the amount of opioid required.

### Calculation and Assessment of Fentanyl Patch Doses

The potency of fentanyl in this noninvasive dosage form, relative to that of other opioids, is not universally understood and appreciated, and the assessment of equianalgesic equivalence is complex.<sup>10</sup> Furthermore, the use of more than one opioid, as well as the history or pattern of use, can increase the difficulty of initiation or titration of fentanyl patch. Pharmacists can support other health care providers in calculating and assessing appropriate doses for fentanyl patch therapy.

### Assessment of Comorbid Conditions and Potential for Drug Interactions

Assessment of the use of fentanyl patch therapy and the dose prescribed must also take into account



comorbid medical conditions (e.g., an underlying pulmonary condition), as well as other factors (e.g., drug interactions or additive effects from other central nervous system depressants<sup>3</sup>) that may increase the potential for serious adverse respiratory effects.

## Patient Education

Pharmacists have an important role in ensuring that patients and family members understand how the product is to be used and are aware of the signs and symptoms of overdose, particularly the requirement that the patch be removed and immediate medical attention sought if signs of overdose occur. The provision of written material is helpful to reinforce verbal instructions. (The monograph for the Duragesic formulation [Janssen Ortho] includes detailed information to be reviewed with patients and provides a patient information sheet.<sup>9</sup>) Pharmacists may also have the opportunity to ask family members if the patient is unknowingly experiencing any dangerous side effects.

## Additional Opportunities

The following are additional areas where pharmacists can assist in ensuring the safe use of fentanyl patches.

- Providing education to other health care providers about the appropriate use of fentanyl patches:
  - indications and contraindications for use
  - unique pharmacokinetics of this dosage form
  - proper handling and disposal
- Reviewing storage and availability of fentanyl patches in hospitals:
  - Safeguards that are in place for the dispensing of other categories of drugs (e.g., unit-dose availability, order verification by pharmacy, preparation of patient-specific doses) are often not in place for opioids and other controlled drugs.
  - Fentanyl patches are not required on an urgent basis for the treatment of acute pain, so the need to have fentanyl patches available in patient care areas should be carefully assessed.
  - Consideration should be given to providing fentanyl patches one dose at a time from the pharmacy department, with a requirement that a pharmacist must review each order.
  - Fentanyl patches should not be available through override of automated dispensing cabinets.

## CONCLUSIONS

Fentanyl patches are a useful and effective treatment option for the management of chronic pain in appropriately selected individuals. However, the safeguards

needed to reduce the potential for harm with this product are not widely understood. Pharmacists, who are charged with responsibility for optimal outcomes of pharmaceutical care, have a key role in enhancing the safe use of this potent analgesic dosage form.

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Medication incidents (including near misses) can be reported to ISMP Canada in 1 of 2 ways:

- through the secure web portal at [http://www.ismp-canada.org/err\\_report.htm](http://www.ismp-canada.org/err_report.htm)
- by telephone at 416.733.3131 or toll-free at 1.866.544.7672 (1.866.54.ISMPC)

