Consequences of unsafe prescribing of transdermal fentanyl

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Pain, both acute and chronic, is a common complaint that must be managed by health care professionals of varying specialties. The assessment and treatment of pain, deemed "the fifth vital sign" by the American Pain Society in 1996, is often inadequate, and the management of patients with chronic pain is frequently difficult. The American Academy of Pain Medicine and the American Pain Society have proposed that opioids be an essential part of pain management plans.[1] Transdermal fentanyl has become popular as a convenient, discrete delivery system of opioid for patients with chronic pain. Safe use of transdermal fentanyl depends on initiation and use in accordance with its product monograph.[2] However, this guidance is often not followed, as clearly shown by Friesen and colleagues in a linked research article.[3]

Many guidelines exist for the use of opioids in treating chronic pain. Most recommend a stepped approach to dosing, starting with a low dosage and escalating based on careful reassessment.[4] There is good reason for this. All opioids share the ability both to depress the central nervous system and to reduce ventilatory drive, particularly in opioid-naive patients. Fairly rapidly after initiation, tolerance develops to the sedating and analgesic effects of the opioid, which frequently prompts an escalation of the dose. However, tolerance to ventilatory effects is more limited, and rapid dose escalation may exceed the ventilatory tolerance threshold, with potentially fatal consequences.

Key points

- New research has highlighted high rates of unsafe prescribing of transdermal fentanyl.
- Transdermal fentanyl is often used as an opioid delivery system for patients with chronic pain because of its reduced dosing frequency, but potential for harm is substantial.
- Opioid-naive patients should not be prescribed transdermal fentanyl because of the inability to predict the drug's effects on central suppression of vital functions and its long duration of effect.
- Also worrisome is the potential for fentanyl abuse and safety concerns for vulnerable family members such as children, since much of the drug remains in the patch after three days of therapeutic use.

The most common opioids for chronic pain include extended-release formulations of morphine, oxycodone and hydromorphone, and the long-acting drug methadone. Some patients prefer to avoid taking pain medications daily or several times daily in oral formulations and switch to alternative delivery systems, most commonly transdermal fentanyl. Use of the fentanyl patch reduces dosing frequency to every three days and provides a steady-state serum concentration, avoiding the peaks and troughs in serum concentrations common with oral agents. Unlike other fentanyl formulations, which are short-acting and used intravenously for the management of acute pain, transdermal fentanyl is indicated exclusively for continuous treatment of chronic pain. Despite subtle differences between guidelines for managing chronic pain, there is consistent agreement that the use of transdermal fentanyl should be strictly limited to opioid-tolerant patients.[4]

Notwithstanding the effectiveness of fentanyl patches for treating chronic pain, both the US Food and Drug Administration[5] and Health Canada[6] have identified safety concerns with these products. Friesen and colleagues[3] report on the substantial iatrogenic dangers associated with unsafe prescribing of transdermal fentanyl, highlighting that 74.1% of patients who were prescribed a fentanyl patch had inadequate prior opioid exposure to warrant initiation of this formulation. Included were patients 65 years of age and older, a group with high rates of comorbid disease that could amplify the consequences of the drug's respiratory depressant effects. Even more alarming is the authors' finding that 26.3% of prescriptions for transdermal fentanyl were to fully opioid-naive patients,[3] which represents a critical prescribing error and system failure.

Physician unfamiliarity with the transdermal delivery system may underpin errors in prescribing. Unlike intravenous and transmucosal fentanyl formulations, which peak quickly and have a half-life of 2–4 hours, the transdermal delivery will not achieve therapeutic serum concentrations until 12–16 hours after application, with time to maximum serum concentration of 36 hours,

although fluctuations may occur up to 72 hours after initiation.[2,7] This delay to onset and peak is due to the need for the applied fentanyl to traverse multiple skin layers before being absorbed into the circulation. In addition, the apparent half-life of fentanyl is substantially longer after removal of the patch (17 h) than after discontinuation of other formulations owing to continued absorption from a fentanyl depot that develops in the lipophilic epidermal tissue.[7]

Perhaps most important, substantial variation between patients in serum fentanyl concentrations occurs during both the initiation phase immediately after application of the patch and after attaining steady-state concentrations. Wide variation in individual fentanyl pharmacodynamics has been implied by evidence that serum concentrations causing inadequate pain control in some patients will lead to hypoventilation in others. This results in a lack of predictability of effect during initiation of transdermal fentanyl and the possibility of unintentional overdose. A recent cohort study showed that patients with chronic pain who were given long-acting opioids were more than twice as likely as those given short-acting opioids to have an unintentional overdose, with more than a fivefold increased risk during the first two weeks of treatment.[8] These findings serve to emphasize the dangers associated with initiation of long-acting opioid formulations. Indeed, methadone, a drug with similar complicated, unpredictable and long-acting pharmacokinetics, has been shown to confer similar risks during initiation of treatment.[9]

Most worrying is the potential for diversion and abuse that exists with transdermal fentanyl, as with all opioids. The diversion or theft of fentanyl patches is now the primary route in which pharmaceutical fentanyl is obtained for abuse purposes.[10] Abuse reportedly includes application of multiple patches, ingestion or rectal insertion of patches, and intravenous injection or insufflation of fentanyl gel removed from the patch reservoir.[11] In addition, between 28% and 84% of the initial drug remains in the device following three days of therapeutic use of a patch. This means there is potential for abuse of fentanyl in a used patch as well as safety concerns for patients and vulnerable family members such as children. Multiple reports of inadvertent pediatric exposure and toxicity highlight the need for appropriate removal and disposal of used patches according to the product monograph.[2]

Although the transdermal route for delivery of fentanyl offers certain advantages for patients and prescribers, unsafe prescribing practices are common and may reflect a lack of familiarity, or lack of appropriate respect for the magnitude of risk of harm, among prescribers. This represents an error related to the axiom of "unknown unknowns" — prescribers do not know what they do not know. Improved prescriber education and implementation of preventive strategies (e.g., electronic medical record prompts and warnings, and prescription monitoring programs) may prove beneficial. As the prevalence of chronic pain and use of opioids continue to increase in Canada, health care practitioners need to be diligent to avoid making an iatrogenic contribution to this public health crisis.

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