Fentanyl Transdermal System: Taking Another Look

Fentanyl transdermal system provides many benefits for management of moderate to severe chronic pain, but this medication can be very dangerous. Errors involving these patches have a heightened risk of significant patient harm.

In 2005, the U.S. Food and Drug Administration (FDA) issued a Public Health Advisory containing important safety information about using fentanyl transdermal patches. Deaths and overdoses have occurred, and the directions for the use of this medication must be followed exactly to prevent death or serious side effects. At the same time as FDA’s advisory, Janssen Pharmaceutica issued an important boxed warning informing healthcare professionals about updates to the clinical pharmacology, contraindications, precautions, dosage, and administration changes for DURAGESIC® (fentanyl transdermal system).

Reports submitted to PA-PSRS and national reporting programs demonstrate problems that have resulted in patient harm. These problems include multiple fentanyl transdermal patches inadvertently placed; concomitant use of transdermal patches with patient-controlled analgesia; inappropriate prescription, particularly with the opioid-naïve population; potential patient abuse of the patch; and lack of patient education, especially regarding administration and storage and disposal.

Background

In 1960, Paul Janssen first synthesized fentanyl on a quest to develop analgesic compounds with a greater potency and safety than the existing narcotic analgesics. Attempts to optimize the molecular configuration of meperidine led to the development of fentanyl, a compound 100 to 300 times more potent than morphine. Fentanyl is an opioid analgesic that interacts predominantly with the opioid mu-receptor binding sites in the brain, spinal cord, and other tissues. Its principal pharmacologic effects are on the central nervous system, and its actions of therapeutic value are analgesia and sedation.

First approved by FDA in 1990 and now available generically, fentanyl transdermal system is a convenient delivery system of a rate-controlled drug (other routes were limited by a short duration of action). Skin permeability studies in the early 1970s verified that the permeation of foreign substances was mediated primarily by diffusion. The main reason for disparities in permeation was the variation in thickness of the stratum corneum. The absorption of fentanyl transdermally remains essentially unchanged from the chest, abdomen, and thigh. The drug passes through the skin and is absorbed into the general circulation by capillaries near the surface of the skin.

Pharmacokinetics

Bioavailability studies report 92% of the dose delivered by fentanyl transdermal system reaches systemic circulation as unchanged fentanyl. Holley and van Steennis found the fentanyl transdermal system to be as effective in obtaining therapeutic serum fentanyl concentrations as a 24-hour continuous, intravenous (IV) infusion of fentanyl at a rate of 100 mcg/hr. Varvel et al. described the skin as both a barrier and a reservoir for the transdermal administration of a drug; these factors (1) cause the drug to be absorbed slowly and released in a sustained manner, and (2) produce a constant serum drug concentration for long periods of time.

Fentanyl plasma concentrations are not measurable until 2 hours after patch application and require 8 to 16 hours until full effects are observed. Steady-state serum levels of fentanyl are maintained for as long as the patches are applied. The patches are re-applied after 72 hours, but the effects are prolonged because fentanyl continues to be absorbed from the skin reservoir. Because of its long delay and decay times, the fentanyl transdermal system is unsuitable

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*For the purposes of this article, the terms fentanyl transdermal system, fentanyl transdermal patch, and fentanyl patch will be used interchangeably.
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for the routine management of short-duration, acute pain states.2,4

Indications
Use of fentanyl transdermal system is indicated in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to a transdermal system dose of 25 mcg/hr (see Table).7,8 Fentanyl transdermal system is contraindicated in patients who are opioid-naïve, patients who are in acute pain, patients who require opioid analgesia for a short period of time, and in patients who suffer only mild pain. It is contraindicated in the management of intermittent or postoperative pain, including use after outpatient or day surgeries.2,7,8 During use of fentanyl transdermal system, a patient may still be able to perceive the presence of pain, but the patient’s tolerance for pain increases, which decreases perception of suffering. Fentanyl transdermal system depresses the respiratory centers, depresses cough reflex, and constricts the pupils.

Respiratory depression is the chief hazard in prescribing fentanyl transdermal system for elderly and debilitated patients, who generally have altered pharmacokinetics due to poor fat stores and muscle wasting.2 The safety of fentanyl transdermal system has not been established in children younger than 2 years old; administration to children 2 years old and older is only indicated if they are opioid-tolerant.

System Structure
Two types of fentanyl transdermal patches are commercially available today — a reservoir patch and a matrix patch. Duragesic manufactured by Janssen, as well as the fentanyl transdermal system by Sandoz, has a reservoir which contains the drug. The fentanyl transdermal system by Mylan Pharmaceuticals Inc. does not contain a reservoir. It is a matrix patch with the drug evenly distributed throughout the adhesive layer. All three patches, however, are packaged with a protective liner, which must be removed and discarded at the time of use.2,7,8 Cutting or damaging the reservoir or matrix fentanyl transdermal patch is against the approved labeling from FDA.1

Reported Adverse Drug Events
Fentanyl is considered a high-alert medication in PA-PSRS, which means that, while not necessarily more prone to medication errors, an error carries greater risk of patient harm or death.9 A variety of fentanyl transdermal system adverse events have been reported to PA-PSRS and national reporting programs. These reports have highlighted the following issues.

Multiple Patches
The majority of the cases reported to PA-PSRS of medication errors involved multiple patches. In a typical scenario, a patient suffering from chronic pain was prescribed fentanyl transdermal patch to be changed every 72 hours. Several days after the patch change was supposed to occur, the patient required transfer to a higher level of care (e.g., intensive care unit [ICU]) because of a compromised respiration rate. After this transfer, multiple fentanyl transdermal patches were found on the patient and removed. Naloxone was administered, and the patient recovered.

Current Analgesic | Daily Dosage (mg/day) | Daily Dosage (mcg/hr)
--- | --- | ---
morphine, oral | 60-134 | 135-224 | 225-314 | 315-404
morphine, intramuscular or intravenous (IV) | 10-22 | 23-37 | 38-52 | 53-67
oxycodeone, oral | 30-67 | 67.5-112 | 112.5-157 | 157.5-202
HYDROMorphOne, oral | 8-17 | 17.1-28 | 28.1-39 | 39.1-51
HYDROMorphOne, IV | 1.5-3.4 | 3.5-5.6 | 5.7-7.9 | 8-10
fentanyl transdermal system | 25 | 50 | 75 | 100

Table. Dose Comparison. This table is not all-inclusive and should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of this table for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdose of the new analgesic agent is possible (see “Dosage and Administration — Discontinuation of Fentanyl Transdermal System” in full prescribing information). Daily dosages depend on multiple patient factors (e.g., age, weight, opioid tolerance, concomitant medication therapy).

Sources:
Janssen Pharmaceuticals. Duragesic® (fentanyl transdermal system) [full prescribing information]. 2005 Jun;
Sandoz Inc. Fentanyl transdermal system [full prescribing information]. 2005 Apr;
Mylan Pharmaceuticals Inc. Fentanyl transdermal system [full prescribing information]. 2005 Dec.
The risk of harm from multiple fentanyl transdermal patches stems from the fact that a significant amount of medication resides in a patch even after the intended period of application had expired. For example, at a delivery rate of 50 mcg/hour for the recommended duration of application of 3 days, 1,400 mcg of fentanyl (28% of the total original fentanyl content) would remain in the Duragesic patch after 72 hours. For a fentanyl transdermal patch from Mylan, approximately 1,500 mcg of fentanyl (29% of the total original fentanyl content) would remain.

Examples reported to PA-PSRS include the following:

A patient was admitted to the hospital from a nursing home with an O2 saturation of 93% on 2 Liters of oxygen. Although the patient had been ordered a fentanyl transdermal patch 75 mcg/hr patch, the skin assessment revealed multiple fentanyl transdermal patches on the patient’s back and chest. All patches except the one ordered were removed and the patient received supportive care and fully recovered.

A patient was prescribed Nitro patch 0.2 mg/hr during the day and a Duragesic patch 25 mcg/hr every 3 days. The Duragesic patch was inadvertently removed in the evening instead of the Nitro patch. Luckily, the patient suffered no ill effects.

A patient was transferred from a nursing home with a Duragesic patch in place but the patient’s documentation lacked the date of the next dose. The patch was later found following a CVP placement procedure, when the dressing was placed on top of the patch.

In another case reported to the USP-ISMP Medication Errors Reporting Program (MERP), an obese woman presented to the emergency department (ED) with chronic pain but failed to mention the fentanyl patch she was wearing. The patient was admitted to a medical unit with orders for a fentanyl patch 50 mcg/hr every 72 hours, which was applied that evening and IV morphine for breakthrough pain. She was later found unresponsive; she was intubated, given naloxone, and transferred to ICU. Later, a nurse found the patch that the patient had applied at home, deep within a skin fold. The patch was removed, and the patient recovered.

One reason for multiple patches being affixed to patients may be that some manufacturers' patches are clear or translucent, which makes them hard to detect, especially on some skin types (see Figure). Although drug name and strength may be printed on the patch, this may not increase visibility sufficiently. This poor visibility of the patches may make it difficult for healthcare practitioners to determine whether or not a patient has a patch affixed to the skin. Poor patch visibility also may hinder the ability of emergency personnel to properly identify and treat patients who suffer a fentanyl overdose. Another reason may be that there is not a good mechanism in place to remind practitioners, patients, and caregivers to remove old patches.

Inappropriate Prescribing
“Off label” use of fentanyl patches has led to patient harm due to inappropriate prescribing. Product labeling states that these patches are for use in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to a 25 mcg/hr fentanyl patch (see Table above). Patients considered opioid tolerant are those who have been taking at least 60 mg of oral morphine daily, 30 mg of oral oxycodone daily, or 8 mg of oral HYDROMorphOne daily (or an equianalgesic dose of another opioid) for a week or longer. Prescribing information also indicates that after the initial patch application, evaluation of the maximum analgesic effect cannot be made until the patch is worn for 72 hours.

Figure. Clear or Translucent Fentanyl Patches.
From left, Jannsen Duragesic, reservoir delivery; Sandoz fentanyl transdermal system, reservoir delivery; and Mylan fentanyl transdermal system, matrix delivery. Images provided courtesy of ISMP.
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at least 24 hours and may take up to 6 days for the patient to reach equilibrium on the new dose. However, adverse event reports indicate that these guidelines are not being followed.

The following example from the MERP supports the need for prescribers who order the fentanyl patch to supply patients with clear and specific verbal and written directions and caution patients to follow these directions exactly. An elderly patient died due to inappropriate prescribing and her subsequent confusion about how to use a fentanyl patch. One week before her death, the patient was prescribed an oral opioid derivative for sciatic pain, of which she took approximately four doses. Still in pain, she consulted her physician by telephone, who prescribed fentanyl 50 mcg/hr patches to be applied every 48 to 72 hours. This patient was considered a non-opioid tolerant patient because she had not received the minimum daily oral dose of 30 mg of oxycodone for a week or longer. She had only taken a total of 20 mg of oxycodone in the entire week. The 48-hour dosing interval was also inappropriate for this elderly patient. It was not questioned. After placing a fentanyl patch on her lower back (i.e., the point of pain), the woman positioned a heating pad on her lower back and went to bed, which was her usual practice but hastened absorption of the medication. She was found dead by a friend two days later.

In another example from the MERP, a hospitalized patient who was opiate-tolerant was prescribed a fentanyl transdermal patch 50 mcg/hr dosage. However, the prescriber adjusted the dose within 72 hours, before the patient was discharged on a 100 mcg/hr dose. At home, the patient experienced somnolence and confusion and fell. She was readmitted to the hospital. If the patient had been maintained at the increased dose through two applications before any further increase in dosage was made on the basis of the average daily use of a supplemental analgesic, this adverse event may have been prevented.

Potential Abuse

Fentanyl transdermal system can be abused in a manner similar to other opioids, legal or illicit. This is a consideration when prescribing, dispensing, or administering. Numerous PA-PSRS reports indicate potential patient abuse issues. Consider the following reports to PA-PSRS:

A patient removed a fentanyl transdermal patch due to itching but upon examination of the patch, it appeared to have been chewed. Patient admitted to eating patches in the past, for which she required naloxone. At the patient’s discharge from the hospital, the patient reported that the fentanyl transdermal patches are “in a safe at home.”

A patient’s wife found a chewed transdermal fentanyl patch in the patient’s coat pocket and threw it out in a basket. Shortly thereafter, the patch was not located when checking the basket. When checking the left anterior chest for the patch, where it had been initially placed, it was found to be missing. Later, the patient left the hospital against medical advice.

Patient Education

Administration procedures. In an error reported to the MERP, an elderly woman was hospitalized after she applied multiple patches at the same time, believing the patches were supposed to be placed “wherever it hurt.” She was brought to the ED because of increased somnolence and markedly reduced respiratory effort. It was then discovered that the patient had applied six fentanyl patches in all.

Storage and disposal. Proper storage and disposal of fentanyl patches is of utmost importance, for example, to protect children from gaining access to this medication. Children who witness their parents applying patches or taking medications could learn by example. Children could equate applying a patch with putting on a sticker, Band-Aid™ or temporary tattoo.

Examples from the MERP include the following:

A 4-year-old child was found dead on the floor of a bedroom near an overturned trashcan that held torn pouches and disposed fentanyl patches. The mother, who suffers from chronic pain due to Crohn’s disease, reported that her son had applied one patch to his leg, but that she did not know how long the patch was in place.

In other cases, one child was accidentally exposed to a fentanyl patch that fell off a family member, and another child removed a fentanyl patch from his sleeping grandmother and applied it to himself. Neither child was seriously hurt.

Other Considerations

Patients who have been prescribed fentanyl transdermal system and develop a fever should be monitored for opioid side effects. Serum fentanyl concentrations increase by one-third for a body temperature
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of 40°C (104°F) due to temperature-dependent increases in fentanyl diffusion from the system and increased skin permeability. Exposure to direct heat sources (e.g., heating pads, saunas, hot tubs, heated water beds) while using a fentanyl transdermal patch may have a sudden and possibly dangerous increase in fentanyl absorption.

Safe Medication Strategies
There are a number of strategies that can assist in the safe use of fentanyl transdermal patches, including the following.

Prescribing
- Prescribe fentanyl patches only for chronic pain and for those patients who are already tolerant to opioid therapy of comparable potency.
- Make sure the dose, dosing interval, and titration prescribed are appropriate for the patient and his or her age and condition.
- Require a pharmacist review when the route or technique of medication is changed.
- Perform skin assessment upon admission to check if patient is wearing any patch.
- Update medication history forms to include prompts for information about transdermal patches.

Administration
- Assess patient’s skin to check if patient is wearing any patch in the ED, upon admission, during routine assessments, and at any change in the level of care.
- Remove the patch backing to expose the adhesive layer.
- Improve methods of documentation and communication about patch location. List patch location and removal on the medication administration record (MAR).
- In facilities with computerized MARs, program patch information into the pharmacy computer system so that these entries automatically appear on the MAR.
- In medication administration policies, include safe medication practices that contain information about transdermal patch application.
- Conduct ongoing education and annual staff competencies on the safe administration of fentanyl transdermal patches.
- Be alert for signs of possible drug-seeking behaviors with these patches.

Patient Education
Fentanyl prescribing information contains a list of 22 points for practitioners to address with patients. Some of this is covered in patient information handed to patients along with their prescription but, all too often, this important information is overlooked or deemed too difficult to read. After reviewing this list (found in the “Precautions” section under “Information for Patients”), practitioners can determine how to best convey the information to patients or their caregivers.

- Supply patients with clear and specific verbal and written directions about the patch usage, and caution patients to follow directions exactly.
- Educate patients to store patches and all other medications in a safe place out of the reach of children.
- Educate patients about the proper disposal of used patches.
- Teach patients to avoid exposure to direct heat sources (e.g., heating pads, saunas, hot tubs, heated water beds) while using the patches, because contact may increase fentanyl absorption.
- Provide a dosing calendar so patients can keep track of the location and time of patch application at home.
- Emphasize the need to remove old patches prior to the application of a new patch.

Notes
5. Holley F, van Steennis C. Postoperative analgesia with fentanyl: pharmacokinetics and pharmacodynamics of constant-rate
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you can’t see can harm you. ISMP Nurse Advise-ERR. 2007
patches…big problems. New safety warnings about fentanyl
patches – part 1. ISMP Med Saf Alert! Community/Ambulatory
12. Institute for Safe Medication Practices (ISMP). Fentanyl trans-
dermal system: unsafe in experienced hands. ISMP Medication

Self Assessment Questions

The following questions about this article may be useful for internal education and assessment.
You may use the following examples or come up with your own.

1. Fentanyl transdermal system’s clinical uses include all
EXCEPT which one of the following?
A. Patients who are already receiving opioid therapy
B. Patients who are suffering from intermittent pain
C. Patients who have demonstrated opioid tolerance
D. Patients who require a total daily dose at least equiva-
tent to a transdermal system dose of 25 mcg/hr

2. Fentanyl transdermal system’s principle pharmacologic
effects are on the central nervous system and its actions of
therapeutic value include analgesia and sedation.
A. True
B. False

3. Fentanyl transdermal system is contraindicated in patients
who are opioid-naive and/or those who are in acute pain.
A. True
B. False

4. How soon after the application of an initial dose of a fentanyl
patch will its full effects be observed?
A. 24 hours
B. 2 to 4 hours
C. 8 to 16 hours
D. Immediately

5. The absorption rate of fentanyl transdermal system is inde-
pendent of patient condition or treatment.
A. True
B. False

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- “Bone Cement Implantation Syndrome” (December 2006)
- “Delays in the OR: Stress between ‘Running Two Rooms’ and ‘Time Outs’” (September 2006)
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