Fentanyl Iontophoretic Transdermal System

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Generic Name: Fentanyl iontophoretic transdermal system
Proprietary Name: Ionsys (The Medicines Company)
Approval Rating: 3S
Therapeutic Class: Opioid analgesics
Similar Drugs: Injectable patient-controlled analgesics
Sound- and/or Look-Alike Names: Fentanyl transdermal patch

INDICATIONS
The fentanyl iontophoretic transdermal system is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization. Patients should be titrated to an acceptable level of analgesia before initiating fentanyl iontophoresis. The system is only for use in patients alert enough and with sufficient cognitive ability to understand the directions for use. The iontophoretic system is not indicated for home use and is inappropriate for use in patients after they have been discharged from the hospital. Use is not recommended in patients younger than 18 years.¹

CLINICAL PHARMACOLOGY
The fentanyl patient-activated transdermal system delivers small doses of fentanyl by iontophoresis. The system utilizes an imperceptible low-intensity direct current to move fentanyl from a hydrogel reservoir into the skin. The preprogrammed, self-contained, self-adhesive unit is about the size of a credit card and is worn on the patient’s upper arm or chest.²,³ The dose is controlled by the amount of electrical current and is designed not to exceed 40 mcg per activation.²,³

The transdermal system uses a 10-minute transdermal infusion for each 40 mcg dose. Drug delivery begins when the electrical current is applied to the transdermal system. This happens after the patient presses the dosing button twice within 3 seconds. Once activated, the system cannot deliver additional

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**PHARMACOKINETICS**

The site of application of the iontophoretic device can influence the pharmacokinetic profile of this transdermal system. However, the pharmacokinetic parameters were similar when the transdermal system was applied to the upper outer arm or chest, the recommended application sites. Application of the iontophoretic device to the lower inner arm resulted in 20% reduced delivery. The impact of application to other sites on the body was not assessed. Peak concentration following a 25 mcg dose is 1.193 mcg/L when the system is applied to the upper outer arm and 1.176 mcg/L when applied to the chest. The area under the curve (AUC$_{24-25}$) was 1.033 mcg•h/L with application to the upper outer arm and 1.015 mcg•h/L with application to the chest. Both peak concentration and AUC$_{24-25}$ were lower when the system was applied to the lower inner arm (peak concentration, 0.859 mcg/L; AUC, 0.757 mcg•h/L). When the system was applied without activating the current, the mean passive absorption rate for fentanyl over 24 hours was 2.3 mcg/h. An average of 57.4 mcg of fentanyl was absorbed. The mean peak serum fentanyl concentration reached at 24.15 hours was 0.06 ng/mL (range, 0.02 to 0.21 ng/mL). The amount of fentanyl absorbed is proportional to the amount of electrical current applied to the iontophoretic system (higher currents are associated with more and lower currents with less fentanyl absorption). When an electrical current of 170 microamps was applied to the system for 10 minutes, 39.5 mcg of fentanyl was absorbed. The amount of fentanyl absorbed from this system increases as a function of time and is independent of both frequency and number of doses. The reason for the increase in absorption is unknown, but may be related to alterations in the skin’s electric conduction properties that may occur as the skin adjusts to the electric current from the system. Administration of a 40 mcg dose with 10-minute applications of various electrical current levels resulted in levels below quantification in some subjects during the first hour of administration, but all participants had measurable levels at 12 to 13 and 23 to 24 hours after application. With repeated administration of the 40 mcg dose over 1 to 3 days, the time to peak concentration was 1 to 2 hours and the half-life was 11.4 to 14.2 hours. A lag of approximately 5 minutes has been observed between the end of the transdermal system dose and the onset of a decline in serum fentanyl concentration. The rate of decline is also slower than that observed after discontinuation of intravenous (IV) administration but is substantially quicker than that observed with the fentanyl transdermal patch, which creates a subcutaneous depot that slowly releases the drug.

Intravenous fentanyl has exhibited a 3-compartment disposition model, with an initial distribution half-life of about 6 minutes, a second distribution half-life of about 1 hour, and a terminal elimination half-life of about 16 hours. Fentanyl accumulates in skeletal muscle and fat and is released slowly into the blood.

Fentanyl metabolism is primarily mediated by cytochrome P450 3A4 (CYP3A4). Most of the dose is excreted in the urine, primarily as metabolites. Less than 10% of the dose is excreted in the urine, primarily as unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Body weight, sex, and race have not been observed to alter the pharmacokinetics of patient-activated transdermal fentanyl. Fentanyl clearance may be reduced and the terminal half-life prolonged in elderly patients.

**COMPARATIVE EFFICACY**

**Indication: Acute Postoperative Pain**

**Studies**

**Drug:** Fentanyl vs Morphine  
**Reference:** Viscusi ER, et al, 2004  
**Study Design:** Randomized, open-label, multicenter study  
**Study Funding:** ALZA Corporation  
**Patients:** 636 adult patients who had undergone major surgery and were comfortable with or without use of IV opioids in the postanesthesia care unit. The most common procedures were lower abdominal (57%) and orthopedic bone (36%). Mean age was about 50 years, and 73% of patients were female.
Intervention: IV morphine (1 mg bolus with a 5-minute lockout; maximum, 10 mg/h) by patient-controlled analgesia (PCA) pump (320 patients) or iontophoretic fentanyl (40 mcg infusion over 10 minutes) by a patient-controlled transdermal system (316 patients). Supplemental morphine or fentanyl IV boluses were administered as rescue medication before and for the first 3 hours after activation of the PCA treatments. Patients then used the assigned PCA treatment without additional analgesics for up to 72 hours. If pain relief was not maintained at a comfortable level, the patient was withdrawn from the study and administered higher doses or additional analgesics to control pain. During the first 24 postoperative hours, the mean amount of medication administered was 1,244 mcg in the fentanyl group and 43.9 mg in the morphine group. The mean number of doses in the first 24 hours was 33.4 in the fentanyl group (range, 3 to 93) and 45.9 in the morphine group (range, 0 to 129). The mean number of doses per patient per hour was 1.39 in the fentanyl group (of 6 available) and 1.91 in the morphine group (of 10 available).

Results

Primary Endpoint(s)
• Success (rating of “excellent” or “good”) on the patient global assessment of the method of pain control was reported by 73.7% (233 of 316) of patients using fentanyl and 76.9% (246 of 320) using morphine (difference, −3.2%; 95% CI, −9.9% to 3.5%; \( P = .36 \)). Similar high rates of “excellent” and “good” ratings were reported for fentanyl and morphine in the subgroup of 275 patients who underwent gynecologic surgery (84.8% vs 83.9%; 95% CI, −7.7% to 9.4%).

Secondary Endpoint(s)
• Early discontinuation occurred in 25.9% of fentanyl-treated patients and 25% of morphine-treated patients \( ( P = 0.78 \) ); withdrawal for inadequate analgesia occurred in 15.2% in the fentanyl group and 10.3% in the morphine group \( ( P = .07 \) ).
• With continued treatment for up to 48 or 72 hours, more than 80% of patient assessments in both groups were “good” or “excellent.”
• Last recorded visual analog scale (VAS) pain intensity scores within the first 24 hours did not differ between the groups (32.7 with fentanyl vs 31.1 with morphine; \( P = .45 \)). Pain intensity scores were similar throughout the first 24 hours of treatment.

Secondary Endpoint(s)
• Supplemental IV opioids were required in 22.8% of fentanyl-treated patients and 27.2% of morphine-treated patients \( ( P = .2 ) \).

Limitations: This was an open-label design study.


Study Design: Randomized, open-label, multicenter study

Study Funding: Ortho-McNeil, Inc

Patients: 799 patients who underwent unilateral total hip replacement and were treated as necessary with IV opioids to achieve comfort (ie, a pain score of 4 or less on an 11-point scale) for at least 30 minutes in a postanesthesia care unit. Median age was 63 years, and 52% of patients were female.

Intervention: Iontophoretic fentanyl 40 mcg per 10-minute infusion/lockout for up to 6 doses per hour (395 patients) or morphine IV 1 mg bolus with 5-minute lockout for up to 10 doses per hour (404 patients) for up to 72 hours. Supplemental IV fentanyl or morphine was permitted during the first 3 hours of the study. Concomitant rofecoxib use was permitted before surgery and daily postoperatively; approximately half of the patients received rofecoxib before it was withdrawn from the market.

Results

Primary Endpoint(s)
• Success (rating of “excellent” or “good”) on the patient global assessment of the method of pain control during the first 24 hours was reported for 83% of patients receiving fentanyl and 82.2% receiving morphine (difference, 0.9%; 95% CI, −4.4% to 6.1%). “Excellent” ratings during the first 24 hours were reported by 50.9% in the fentanyl group compared with 35.9% in the morphine group.

Secondary Endpoint(s)
• Mean last pain intensity score on an 11-point VAS was 3 with both therapies (difference, 0; 95% CI, −0.33 to 0.33); similar pain intensity scores were reported throughout the 24-hour study period.
• Withdrawal from the study for inadequate analgesia was more common with fentanyl (11.1% vs 5.4%; \( P = .004 \)), but overall withdrawal rates did not differ (15.7% with fentanyl and 14.1% with morphine; \( P = .552 \)).
• Supplemental analgesia during the first 3 hours was required by 17% of patients in the fentanyl group and 14.1% in the morphine group \( ( P = .283 ) \).
Endpoint(s)

- Patient evaluation of ease of use/convenience of the methods using the 28-question Patient Ease-of-Care Questionnaire, completed upon study completion or early withdrawal, yielded a higher response rate for ease of care with fentanyl (42.8% vs 27.2%; \(P < .001\)).

- Nurse evaluation of time involved, convenience, and satisfaction with the system using a 22-question Ease-of-Care Questionnaire after at least 10 patients or the last patient completed the study yielded a higher response rate for ease of care for nurses caring for patients treated with fentanyl than nurses caring for patients treated with morphine (79.7% vs 54.8%; \(P < .001\)).

- Physical therapy evaluation after each session assessing satisfaction with the analgesic method and ease with which they completed tasks and attained session goals using a 22-question Ease-of-Care Questionnaire also yielded better response rates for ease of care with fentanyl (82.6% vs 55.1%; \(P < .001\)).

- Adverse events were similar, although patients treated with morphine plus rofecoxib experienced more adverse events than those treated with fentanyl plus rofecoxib.

Comments: System-related events that interrupted pain control occurred more often with the morphine PCA (11.6% vs 5.8%; \(P = .004\)).

Limitations: Withdrawal of rofecoxib from the study protocol halfway through the study resulted in differences in background therapy among study participants. Although differences in the last pain scores between fentanyl and morphine were not observed regardless of concomitant rofecoxib use, more patients in the fentanyl group than the morphine group who did not receive rofecoxib withdrew from the study because of inadequate analgesia (\(P = .024\)). Conversely, more patients who received morphine concurrently with rofecoxib than received fentanyl with rofecoxib withdrew due to adverse events (7.4% vs 1%; \(P = .002\)).


Study Design: Randomized, open-label, multicenter study

Study Funding: Ortho-McNeil, Inc

Patients: 506 patients who underwent abdominal or pelvic surgery and were titrated to comfort (pain score of 4 or less on an 11-point pain scale) using IV bolus opioid doses in the postanesthesia care unit. Mean age was 50.3 years, and 66% underwent pelvic surgical procedures.

Intervention: Iontophoretic fentanyl 40 mcg/dose, up to 6 doses per hour (252 patients) or morphine IV PCA 1 mg/dose, up to 10 doses per hour (254 patients). Supplemental IV fentanyl or morphine was permitted during the first 3 hours; patients requesting additional analgesia more than 3 hours after enrollment were withdrawn for inadequate analgesia.

Results

Primary Endpoint(s)

- Rating of “excellent” or “good” on the patient global assessment of the pain control method in the first 24 hours of treatment was reported by 84.9% of patients treated with fentanyl and 84.3% of patients treated with morphine (difference, 0.6%; 95% CI, −5.7% to 7%). More patients in the fentanyl group rated the method “excellent” (50.0% vs 40.2%; \(P = .039\)).

Secondary Endpoint(s)

- Mean last pain intensity score in the first 24 hours was 3 with fentanyl and 2.9 with morphine (difference, 0.1; 95% CI, −0.28 to 0.43). Mean score at the last observation during the 72-hour study period was also observed (2.6 with fentanyl and 2.5 with morphine; difference, 0.1; 95% CI, −0.27 to 0.47).

- Supplemental analgesia during the first 3 hours was administered to 20.6% of patients in the fentanyl group compared with 12.2% in the morphine group (\(P = .011\)).

- Withdrawal for any reason occurred in 16.7% of patients treated with fentanyl and 11.8% of patients treated with morphine (\(P = .128\)).

- Withdrawal for inadequate analgesia occurred in 9.1% and 2.8% of patients treated with fentanyl and morphine, respectively (\(P = .002\)).

Endpoint(s)

- Ease-of-care ratings by patients favored fentanyl (overall scores of 4.47 with fentanyl vs 4.18 with morphine; \(P < .001\)).

- Ease-of-care ratings from nurses also favored fentanyl (\(P < .001\)).

- Adverse events were similar in the 2 treatment groups. There was no difference in the incidence of withdrawal for adverse events (5.6% with fentanyl and 7.5% with morphine; \(P = .472\)).

Limitations: This was an open-label design study.
Reference: Grond S, et al., 2007

Study Design: Randomized, open-label, multicenter study

Study Funding: Janssen-Cilag NV

Patients: 660 patients who underwent abdominal or orthopedic surgery and were titrated to comfort (pain score of 4 or less on an 11-point pain scale) using IV bolus opioid doses in the postanesthesia care unit. Mean age was 53.3 years and 57% of patients were female. The most common surgical sites were lower abdominal, hip, spinal, pelvic, and upper abdominal.

Intervention: Iontophoretic fentanyl 40 mcg over 10 minutes, up to 6 doses per hour (325 patients), or morphine IV PCA per institution policy, up to 20 mg per 2 hours or 240 mg per 24 hours (335 patients) for up to 72 hours. Morphine doses ranged from 1 to 3 mg, with lockout intervals ranging from 5 to 20 minutes. Supplemental IV morphine was available during the first 3 hours; patients requiring supplemental opioids after the first 3 hours were discontinued from the study for inadequate analgesia. Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and COX-2 inhibitors were permitted.

Results

Primary Endpoint(s)
- Rating of “excellent” or “good” on the patient global assessment of the pain control method during the first 24 hours was reported by 86.2% of patients receiving fentanyl and 87.5% receiving morphine (95% CI, −6.5% to 3.9%). More patients in the fentanyl group reported a rating of “excellent” than in the morphine group (39.1% vs 29.9%). Patient ratings at 24 hours and investigator ratings at 24, 48, and 72 hours did not differ between groups. Patient and investigator ratings were also similar for fentanyl and morphine regardless of surgical site, except for knee surgery, for which morphine rated higher.

Secondary Endpoint(s)
- Mean pain intensity score at the last assessment after the first 24 hours was 2.5 with fentanyl and 2.4 with morphine (95% CI, −0.18 to 0.38).
- Mean pain intensity score at the last assessment was 1.8 with fentanyl and 1.9 with morphine (95% CI, −0.38 to 0.18).
- Mean total number of doses per patient was 46.2 in the fentanyl group; mean dose delivered was 1.9 mg of fentanyl over 72 hours and 54.7 mg of morphine over 72 hours.
- Withdrawal due to inadequate analgesia occurred in 3.4% in the fentanyl group and 2.4% in the morphine group (95% CI, −1.6 to 3.6); withdrawal for any reason occurred in 11.4% in the fentanyl group and 11% in the morphine group (95% CI, −4.5 to 5.2).
- Supplement opioids were administered during the first 3 hours in 11% of patients in both groups; more patients undergoing knee surgery required supplemental opioids (45% of fentanyl-treated patients and 32% of morphine-treated patients).

Limitations:
- This was an open-label design study conducted exclusively in Europe. Morphine PCA dosing was not standardized.

Drug: Fentanyl vs Placebo

Reference: Chelly JE, et al., 2004

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: ALZA Corporation

Patients: 205 patients with postoperative pain following major abdominal, orthopedic, or thoracic surgery; 189 patients were considered evaluable (142 in the fentanyl group and 47 in the placebo group). Most patients were female (68.8%) and lower abdominal surgical procedures were most common (51.3%).

Intervention: Iontophoretic transdermal fentanyl administered as 40 mcg over 10 minutes on demand or an identical placebo system that did not deliver drug.
Results

Primary Endpoint(s)

- The percentage of patients withdrawn from the study because of inadequate analgesia after completing at least 3 hours of treatment was 25.4% in the fentanyl group and 40.4% in the placebo group ($P < .05$).

Secondary Endpoint(s)

- Mean last VAS pain intensity score was lower with fentanyl than placebo (30.9 in the fentanyl group compared with 40.8 in the placebo group; $P = .047$).
- The mean global assessment score of the method of pain relief was greater with fentanyl than placebo as assessed by the patients (3.0 vs 2.6; $P = .047$) and by the investigators (3.1 vs 2.6; $P = .007$).

Endpoint(s)

- Good system adherence (at least 90% adherence with no edges unattached) was achieved in 90% of patients. The system fell off 3 patients (1.5%) and 4 required additional taping.

Limitations: A high proportion of patients entered the study with pain scores of 75 or greater (19%) and a disproportionate number (5:1) were randomized to the fentanyl group; patients with pain scores of 75 or greater were more likely to withdraw from the study early for inadequate pain control, possibly underestimating the efficacy of the fentanyl system relative to placebo. An adequate level of pain relief should be achieved before initiating PCA.


Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: ALZA Corporation

Patients: 484 patients undergoing general or regional anesthesia for major abdominal, orthopedic, or thoracic surgery. The majority of patients were female (70%) and were undergoing lower abdominal (48%) or orthopedic bone (46%) procedures.

Intervention: All patients received IV opioids in the postanesthesia care unit for initial pain relief. Thirty minutes after opioid administration, patients with pain scores less than 5 (on an 11-point scale, with 0 defined as the absence of pain and 10 as the worst possible pain) were randomized to treatment with iontophoretic transdermal fentanyl 40 mcg per dose (244 patients) or an identical placebo system (240 patients). Rescue IV fentanyl was permitted during the first 3 hours after system application.

Patients who felt their pain was not adequately controlled could withdraw from the study at any time.

Results

Primary Endpoint(s)

- The proportion of patients who withdrew from the study because of inadequate pain relief during the 24-hour treatment period was 60% in the placebo group compared with 28.7% in the fentanyl group ($P < .001$). The mean duration of treatment prior to withdrawal was 7.3 hours in the fentanyl group and 6.5 hours in the placebo group.

Secondary Endpoint(s)

- Withdrawal from the study for any reason occurred in 68.3% in the placebo group compared with 36.9% in the fentanyl group ($P < .001$).
- Rescue medication was used in the first 3 hours by 57.5% of placebo recipients compared with 45.5% of the fentanyl-treated patients ($P = .008$).
- Mean pain intensity score was higher in the placebo group at the last pain assessment (3.5 vs 5.4; $P < .001$) and throughout the 24-hour treatment period.
- More “excellent” ratings were given to the fentanyl system in both the patient global assessment (39.8% vs 14.6%; $P < .001$) and investigator global assessment (47.5% vs 20.8%; $P < .001$).

Endpoint(s)

- Patients reported the system was very convenient (79.8%) and very easy to use (87%), although only 32.1% of the placebo group reported being very satisfied with the pain management provided by the system compared with 61.5% of the patients in the fentanyl group.

Reference: Koo PJ, et al, 2005

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: ALZA Corporation

Patients: 439 postoperative patients.

Intervention: Iontophoretic fentanyl 40 mcg per dose (235 patients) or an identical placebo system (204 patients).

Results

Primary Endpoint(s)

- Discontinuation because of inadequate pain relief occurred in 27.2% (64 of 235) of fentanyl-treated patients compared with 56.9% (116 of 204) of placebo-treated patients ($P < .001$).
Secondary Endpoint(s)
- Rescue IV fentanyl was administered within the first 3 hours in 45% of patients in the fentanyl group compared with 52% in the placebo group.
- Pain management goals were reached for 65% of patients treated with fentanyl compared with 37% treated with placebo ($P < .001$).
- Mean pain intensity score at 24 hours or at discontinuation of therapy was 3.4 in the fentanyl group and 5.3 in the placebo group (on a verbal rating scale from 0 to 10; $P < .001$).
- Patient and investigator global assessments also favored the fentanyl system for successful pain control ($P < .001$).

Comments: Similar results were reported for 2 additional studies with similar study design. In a study including 189 postoperative patients, 25% (36 of 142) of fentanyl-treated patients withdrew compared with 40% (19 of 47) of placebo-treated patients due to inadequate analgesia ($P = .049$). Final mean pain intensity score at 24 hours or at discontinuation of treatment was 31 in the fentanyl group and 41 in the placebo group (on a VAS from 0 to 100 mm; $P = .474$). Rescue IV fentanyl was administered within the first 3 hours in 55% of patients in the fentanyl group compared with 58% in the placebo group. In the other study including 99 postoperative patients, 8% (6 of 77) treated with fentanyl withdrew due to inadequate analgesia compared with 41% (9 of 22) treated with placebo ($P < .001$). Final mean pain intensity score at 24 hours or at discontinuation of treatment was 21 in the fentanyl group and 37 in the placebo group (on a VAS from 0 to 100 mm; $P < .001$). Rescue IV fentanyl was administered within the first 3 hours in 34% of patients in the fentanyl group compared with 36% in the placebo group. Overall in these 3 studies, patients who completed treatment for 24 hours with the fentanyl system used a mean of 29 doses per patient (range, 0 to 93 doses). The majority of patients (56.5%) used between 11 and 50 doses. One percent of patients required a second system within 24 hours, after exhausting the first system.

Limitations: Results from these placebo-controlled studies have not been published, but some of these data are included in the product labeling.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications
The fentanyl iontophoretic transdermal system is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma, known or suspected paralytic ileus or gastrointestinal obstruction, or known hypersensitivity to fentanyl, cetylpyridinium chloride (eg, Cepacol), or any components of the system (citric acid, polacrilin, polyvinyl alcohol, sodium citrate, sodium chloride, and sodium hydroxide).

Warnings and Precautions
The warnings and precautions for this dosage form are similar to those with other fentanyl dosage forms and include boxed warnings regarding inadvertent exposure, life-threatening respiratory depression, use only in a hospital setting and through a Risk Evaluation and Mitigation Strategy (REMS) program, accidental exposure, addiction and abuse, and CYP3A4 drug interactions. Unlike the transdermal patch and transmucosal lozenge, this dosage form is not restricted to patients with preexisting opioid tolerance. The dose released with this dosage form is for the treatment of acute pain and may not provide adequate analgesia for patients with preexisting opioid tolerance. Patients on chronic opioid therapy or with a history of opioid abuse should be evaluated frequently to make sure they are receiving adequate analgesia with the transdermal iontophoretic system.

Patients receiving treatment with fentanyl iontophoretic systems should be under supervision of medical personnel with expertise in the detection and management of respiratory depression, including airway management and the use of opioid antagonists. Patients experiencing adverse effects, including overdose, will require continued monitoring after removal of the system because serum fentanyl levels gradually decline.

As with other forms of PCA, only the patient should activate the fentanyl iontophoretic transdermal system to avoid potential overdosing. More than 1 system should not be applied to a patient at the same time.

Accidental ingestion or contact with mucous membranes, or unintended exposure to the fentanyl hydrogel, could lead to absorption of a potentially lethal dose of fentanyl. The hydrogel should not come into contact with fingers or mouth. If the fentanyl
hydrogel becomes separated from the system, contact can be harmful. If the hydrogel becomes separated from the system during removal, gloves or tweezers should be used to remove the hydrogel from the skin. The affected area of the skin should be thoroughly flushed with water. Soap, alcohol, or other solvents should not be used to remove the hydrogel, as they may enhance the ability of fentanyl to penetrate the skin. If the system falls off, the entire system should be collected and properly disposed of in accordance with state and federal laws and hospital policies. Prior to discharge from the hospital, medical personnel must remove the system and dispose of it properly. The fentanyl iontophoretic system is only available through a restricted REMS program due to the risk of respiratory depression associated with accidental exposure.

Respiratory depression can occur throughout the therapeutic range of fentanyl serum concentrations that may occur at any time during therapy, particularly in patients with an underlying pulmonary condition or who are receiving doses of opioids or other central nervous system (CNS) drugs associated with hypventilation in addition to the fentanyl. The respiratory effects of fentanyl should be monitored by clinical evaluation, including oxygen saturation, respiratory rate, and degree of sedation. The fentanyl iontophoretic system should be used with caution in patients with preexisting medical conditions predisposing them to hypventilation. Patients with hepatic and/or renal impairment should be monitored for signs of sedation and respiratory depression.

The fentanyl iontophoretic system should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention, such as patients with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. The fentanyl system should be used with caution in patients with brain tumors. Patients with seizure disorder may also be at increased risk for seizures; patients should be monitored for worsening seizure control while receiving fentanyl therapy.

Fentanyl may produce bradycardia in some patients. The fentanyl iontophoretic system should be used with caution in patients with bradyarythmias. Patients should also be monitored for hypotension during dose initiation; avoid use in patients with circulatory shock.

Patients with biliary tract disease, including acute pancreatitis, should be monitored for worsening symptoms.

The system should be applied to intact, nonirritated, and nonirradiated skin on the upper outer arm or chest. Application to the inner lower arm resulted in less fentanyl absorption. Application to other sites, such as the legs or abdomen, has not been studied. Topical skin reactions (erythema, sweating, vesicles, papules/pustules) may occur after removal of the fentanyl system. Such reactions are typically limited to the application-site area and resolve without treatment. If a severe skin reaction is observed, the system should be removed and fentanyl iontophoretic therapy discontinued.

The fentanyl system contains metal parts and should be removed prior to a magnetic resonance imaging (MRI) procedure to avoid injury to the patient and damage to the system. The system should also be removed prior to cardioversion, defibrillation, x-ray, computed tomography (CT), or diathermy to avoid damage to the system from the strong electromagnetic fields associated with these procedures. The system also contains radioopaque components that may interfere with an x-ray or CT scan. Avoid contact with synthetic materials (such as carpeted flooring) while assembling the system, and avoid exposing the system to electronic security systems to reduce possibility of damage to the system. Use of the system near communications equipment or a radiofrequency identification (RFID) transmitter can also damage the system and may require separation by 0.12 to 23 meters, depending on the rated maximum output power and frequency of the transmitter. The low-level electrical current provided by the system does not result in electromagnetic interference with other electromechanical devices such as pacemakers or electrical monitoring equipment.

In elderly patients 65 years and older, no overall differences in safety or effectiveness were observed with the fentanyl system compared with younger subjects. The incidence of hypotension, confusion, hypokalemia, hypoxia, and hypoventilation was increased in elderly patients compared with patients 18 to 64 years of age.

The fentanyl iontophoretic system is not recommended for use in pediatric patients. Safety and efficacy have not been adequately studied in patients younger than 18 years.

There are no studies assessing the fentanyl iontophoretic system in pregnant women. Use of the system is not recommended for analgesia during labor and delivery, as fentanyl readily crosses the placenta to the fetus.
Fentanyl is excreted in low levels in human milk. The potential risk of sedation and/or respiratory depression in breast-feeding infants should be considered along with the importance of fentanyl to the mother and the potential health benefits associated with breast-feeding.1

**ADVERSE REACTIONS**

The most common adverse reactions with the patient-activated transdermal system included nausea, fever, application-site reactions (eg, erythema, itching, vesicles), vomiting, headache, anemia, pruritus, dizziness, hypotension, constipation, hypoxia, and insomnia.1,15 The incidence of adverse effects from 3 studies comparing fentanyl with a morphine PCA are summarized in Table 1. Three studies comparing fentanyl with placebo are summarized in Table 2.

Skin reactions have generally been mild to moderate. Erythema was present upon system removal in approximately half of fentanyl-treated patients. Erythema at the application site was generally mild, resembling a sunburn or tanning marks, and resolved within 4 weeks.2,3 Erythema at the application site was observed upon removal of the system in 44.8% of fentanyl-treated patients compared with 31.4% of patients exposed to the placebo transdermal system.3

**DRUG INTERACTIONS**

Drug interactions associated with use of this fentanyl delivery system are the same as with other methods of fentanyl delivery. CNS depressants, including alcohol, other opioids, illicit drugs, sedatives, hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, and sedating antihistamines, may have additive CNS effects. Hypotension, profound sedation, respiratory depression, coma, or death may result. Patients should be closely monitored and dosages of concomitant medications adjusted as needed.1

Fentanyl is primarily metabolized via the CYP3A4 enzyme. Coadministration with CYP3A4 inducers (eg, rifampin, carbamazepine, phenytoin, St. John’s Wort) may increase fentanyl clearance and reduce the efficacy of the fentanyl iontophoretic system. Coadministration with CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, ritonavir) may reduce fentanyl clearance, resulting in increased or prolonged adverse effects.1

Fentanyl iontophoretic system use should be avoided in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping an MAOI.1 Use with mixed agonist/antagonist and partial agonist analgesics should also be avoided, as these may reduce the analgesic effects of fentanyl or precipitate withdrawal.1

### Table 1. Adverse reactions in 3 studies comparing patient-activated fentanyl and morphine PCA10

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Fentanyl (n = 963)</th>
<th>Morphine (n = 978)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>39.4%</td>
<td>43%</td>
</tr>
<tr>
<td>Fever</td>
<td>23.4%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>11.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.3%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Application-site reaction (erythema)</td>
<td>6.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Application-site reaction (itching)</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Note: PCA = patient-controlled analgesia.

### Table 2. Adverse effects in 3 placebo-controlled studies1

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Fentanyl (n = 475)</th>
<th>Placebo (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>39%</td>
<td>22%</td>
</tr>
<tr>
<td>Application-site reaction (erythema)</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Note: PCA = patient-controlled analgesia.
Fentanyl can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Medications with anticholinergic properties may result in increased risk of urinary retention and/or constipation.1

RECOMMENDED MONITORING

Patients should be monitored for pain relief, as well as severe opioid adverse reactions (eg, respiratory depression, hypotension, sedation).

DOsing

Prior to initiation of therapy with the fentanyl iontophoretic system, bolus doses of opioid analgesics should be administered to achieve comfort.1,5 Access to supplemental analgesia should be available during treatment with the fentanyl system.1 Only 1 fentanyl iontophoretic system should be applied at a time.1 Gloves should always be worn when handling the system.1

The system must be assembled prior to application. The controller and drug unit are supplied in a single tray. Both components must be removed from the tray and aligned and snapped together. Once assembled, the controller will complete a short self-test during which it will emit one audible beep, the red light will blink once, and the digital display will flash “88.” After the self-test, the display will show “0” and a green light will blink at a slow rate to indicate the unit is ready for application.1

The system-activated fentanyl transdermal system device should be applied to clean, dry, nonirritated, nonirradiated, intact skin on the upper outer arm or chest. The application site should be prepared by clipping, but not shaving, any hair in the area and cleansing the site with a sterile alcohol wipe. The system is applied by removing the clear plastic liner from the bottom of the device, placing the device on the patient, and applying pressure for 15 seconds. If adherence is not complete, the device may be secured with nonallergenic tape along the edges; avoid taping over the button, light, and digital display.1,5

Only the patient should administer doses from the fentanyl system. The system provides a 40 mcg dose per activation. Each dose is delivered over a 10-minute period. To initiate administration of a dose, the patient must press and release the button twice within 3 seconds. A single audible beep indicates the start of delivery of each dose. A green light will start blinking rapidly and the digital display will alternate between a walking circle and the number of doses delivered. After completion of the 10-minute period of administration, the green light will blink at a slow rate and the display will show the number of doses delivered.1 A health care professional must observe the first dose to ensure the patient correctly operates the system and that the device is working properly.1 A maximum of six 40 mcg doses per hour can be administered with the system. The maximum amount of fentanyl that can be delivered from one system over 24 hours is 3.2 mg (80 doses). Each system operates for 24 hours or until 80 doses have been administered, whichever occurs first; after that time, the unit will not deliver any additional doses and the light and audible beep will not function, but the digital display will continue to show the number of doses delivered for an additional 12 hours. Up to 3 consecutive systems may be used sequentially, for a maximum of 72 hours of therapy, for acute postoperative pain.1 If treatment for longer than 24 hours or more than 80 doses is required, a different application site should be selected for each successive system.1,5 Medical personnel must remove the system and dispose of it properly prior to patient discharge from the hospital.1

The system should be removed, using gloves, by gently lifting the red tab and loosening the system from the skin. Both hydrogels should remain with the removed system. If one of the hydrogels becomes separated from the system, gloves or tweezers should be used to remove the hydrogel from the skin. The fentanyl-containing portions of the system (hydrogels) should be discarded in accordance with state and federal regulations for controlled substances. To dispose of the system, pull the red tab to separate the bottom housing from the top housing. The red bottom hydrogel-containing housing should be folded in half, with the sticky side facing in, and disposed of in accordance with the institution’s policies for disposal of schedule II drugs or by flushing it down the toilet. The top housing, which contains electronics, should be disposed of according to hospital procedures for battery-containing waste.1

PRODUCT AVAILABILITY

ALZA Corporation received US Food and Drug Administration (FDA) approval for the fentanyl iontophoretic transdermal system in May 2006, but the system was not marketed in the United States due to stability issues identified after approval.17,18 Following reformulation of the device into 2 separate components and development of an REMS, The Medicines Company received FDA approval for the system on April 30, 2015.19 It is supplied packaged in a sealed tray.
containing 1 controller unit and 1 drug unit within a foil pouch. Six sealed trays are supplied per carton. Each system supplies up to 80 doses (40 mcg each, or a 24-hour supply). The fentanyl iontophoretic system should be stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). Each drug unit contains 10.8 mg of fentanyl hydrochloride (equivalent to 9.7 mg of fentanyl) plus cetylpyridinium chloride, citric acid, polacrilin, polyvinyl alcohol, sodium citrate, sodium chloride, sodium hydroxide, and purified water. The system is composed of a plastic top housing that contains a 3-volt lithium battery and electronics and a red plastic bottom housing that contains 2 hydrogel reservoirs and a polysisobutylene skin adhesive. The anode hydrogel located under the dosing button contains fentanyl hydrochloride along with inactive ingredients. The cathode hydrogel contains only inactive ingredients. A siliconized clear, plastic release liner covers the hydrogels and must be removed and discarded prior to placement on the skin.

**DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

An REMS was required for approval of the fentanyl iontophoretic system due to concerns regarding the risk of respiratory depression resulting from accidental exposure in a health care worker or other person for whom it was not prescribed. To mitigate these risks, health care settings that dispense the system must be certified and the drug can only be dispensed to patients in select health care settings.

Fentanyl is a schedule II controlled substance.

**CONCLUSION**

The fentanyl patient-activated transdermal system offers a unique delivery system for PCA. It can be used in most cases in which an IV opioid PCA is currently in use and has demonstrated equivalent therapeutic activity. This iontophoretic system is not a replacement for the transdermal fentanyl patch.

**REFERENCES**

1. Ionsys (fentanyl iontophoretic transdermal system) [prescribing information]. Parsippany, NJ: The Medicines Company; April 2015.


Continuing Education Case Study Quiz

Goal—The goal of this activity is to educate pharmacists about the use of the fentanyl iontophoretic transdermal system in the management of acute postoperative pain.

Objectives—At the completion of this activity, the reader will be able to:
1. Describe the pharmacology and pharmacokinetics of the fentanyl iontophoretic transdermal system.
2. Discuss the risks associated with the use of the fentanyl iontophoretic transdermal system.
3. Discuss the potential benefit of the fentanyl iontophoretic transdermal system for an individual patient.
4. Apply the information on the use of the fentanyl iontophoretic transdermal system to a case study.

Key Words—fentanyl, iontophoresis, patient-controlled analgesia, new drugs

This CE activity is jointly provided by ProCE, Inc. and Hospital Pharmacy. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-16-002-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 1-01-2016). This CE activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Completion of the evaluation and the post-test with a score of 70% or higher are required to receive CE credit. No partial credit will be given.

Faculty: Dennis J. Cada, PharmD, FASHP, FASCP (Editor), Founder and Contributing Editor, The Formulary; Terri L. Levien, PharmD, Clinical Professor, College of Pharmacy, Washington State University, and Danial E. Baker, PharmD, FASHP, FASCP, Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University. The authors indicate no relationships that could be perceived as a conflict of interest. This activity is self-funded by Hospital Pharmacy.

Release Date: January 1, 2016
Expiration Date: January 1, 2018

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• Click to access the activity page to enroll and complete the Post-Test and Evaluation

For questions related to registering for and obtaining CE credit, contact ProCE at 630-540-2848 or Info@ProCE.com.

1. The fentanyl iontophoretic transdermal system is US Food and Drug Administration (FDA)—approved for:
   A. Initial postoperative analgesia.
   B. The management of acute or chronic pain in patients with preexisting opioid tolerance.
   C. The management of acute postoperative pain following discharge from an outpatient surgical center.
   D. The short-term management of acute postoperative pain during hospitalization.

2. Fentanyl is delivered from the iontophoretic transdermal system via:
   A. Chemical enhancer that increases skin permeability and increases transdermal absorption.
   B. Low-intensity direct current that moves fentanyl from a hydrogel reservoir into the skin.
   C. Passive diffusion into the stratum corneum that serves as a sustained release reservoir.
   D. Short, high-voltage pulses that drive fentanyl from a hydrogel reservoir into the skin.
Continuing Education Case Study Quiz

3. How long is the fentanyl iontophoretic system designed to operate after its first activation?
   A. 6 hours
   B. 12 hours
   C. 24 hours
   D. 3 days

4. What dose is delivered with each activation of the fentanyl iontophoretic transdermal system?
   A. 10 mcg
   B. 20 mcg
   C. 40 mcg
   D. 3.2 mg

5. How long does it take for the entire dose to be delivered after the patient activates the system?
   A. 10 seconds
   B. 1 minute
   C. 10 minutes
   D. 60 minutes

6. In clinical trials comparing the fentanyl iontophoretic transdermal system and morphine intravenous patient-controlled analgesia, success, defined as a rating of “excellent” or “good” on the patient global assessment of the method of pain control, was:
   A. More common with fentanyl.
   B. More common with morphine.
   C. Not reported for either fentanyl or morphine.
   D. Reported with similar frequency with fentanyl and morphine.

7. Which of the following medical conditions does NOT require additional caution with the use of the fentanyl iontophoretic transdermal system for the treatment of pain?
   A. A seizure disorder
   B. Acute pancreatitis
   C. Bradycardia
   D. Osteoarthritis

8. Which of the following may reduce fentanyl clearance resulting in increased adverse effects?
   A. A CYP3A4 inducer such as carbamazepine
   B. A CYP3A4 inhibitor such as clarithromycin
   C. An anticholinergic such as diphenhydramine
   D. A P-glycoprotein inhibitor such as verapamil

9. When should therapy with the fentanyl iontophoretic transdermal system be initiated in K.J.?
   A. While her pain is controlled with the intravenous morphine
   B. As soon as her pain starts to return
   C. No sooner than 2 hours after the last bolus morphine dose
   D. When her pain reaches at least a 5 on a 0 to 10 point visual analog scale

10. Where should the fentanyl iontophoretic transdermal system be applied on K.J.?
    A. The inner lower arm or outer upper arm
    B. The outer upper arm or abdomen
    C. The neck or chest
    D. The upper outer arm or chest

11. K.J. has pressed and released the button twice within 3 seconds to activate a dose but is concerned the device isn’t doing anything. How can one tell if a dose is being delivered?
    A. She should feel a tingling sensation at the application site while the dose is being delivered.
    B. An audible beep should be heard throughout the delivery, accompanied by a slowly blinking green light and a digital display of the number of doses delivered.
    C. An audible beep should have indicated the start of delivery, and during delivery a green light should blink rapidly and the digital display should alternate between a walking circle and the number of doses delivered.

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Case History
K.J. is a 56-year-old female patient undergoing anterior cervical discectomy with fusion. She has hypertension and hypercholesterolemia, controlled with lisinopril 40 mg once daily and atorvastatin 40 mg once daily. Her previous medications also included naproxen. She has no known drug allergies and has normal renal and hepatic function. Following surgery, her pain was managed with intravenous morphine until transfer to the postoperative floor. Her surgeon has ordered the fentanyl iontophoretic transdermal system for one day to facilitate rapid ambulation and discharge.
D. An audible beep should have indicated the start of delivery, and during delivery a green light should blink slowly and the digital display should rapidly blink the number of doses remaining.

12. The side effects most commonly reported in patients treated with the fentanyl iontophoretic transdermal system are:
   A. Hypertension, nausea, dizziness, and cough.
   B. Hypotension, hyperkalemia, nausea, and dizziness.
   C. Nausea, vomiting, diarrhea, and headache.
   D. Nausea, vomiting, fever, and application-site reactions.

13. K.J. requires an x-ray prior to discharge. Which of the following statements is true?
   A. The system can be safely left in place during an x-ray, computed tomography, or magnetic resonance imaging procedure.
   B. The system can be safely left in place during an x-ray, but must be removed prior to a computed tomography or magnetic resonance imaging procedure.
   C. The system must be removed prior to x-ray to avoid damage to the system.
   D. The system must be removed prior to x-ray to avoid injury to the patient.

14. K.J.’s nurse notes that the hydrogel became separated from the unit during removal of the system from K.J.’s skin? How should she remove the hydrogel?
   A. The hydrogel should be removed using gloves or tweezers.
   B. The hydrogel should be rubbed off with an alcohol swab.
   C. The hydrogel should be scraped from the skin with her fingernail.
   D. The hydrogel does not need to be removed since it does not contain fentanyl.

15. Following initiation of the fentanyl iontophoretic transdermal system in another patient, it is realized that the patient has preexisting opioid tolerance. Which of the following best describes the recommended course of action?
   A. Apply two systems concurrently to make sure sufficient fentanyl is delivered.
   B. Discontinue therapy immediately as the patient is expected to be more sensitive to the effects of the fentanyl.
   C. Discontinue therapy immediately as the patient is not a candidate for any opioid therapy.
   D. Monitor the patient closely to make sure they are receiving adequate analgesia.