

A patient-activated iontophoretic transdermal system for acute pain management with fentanyl hydrochloride: Overview and applications

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ABSTRACT

Opioid administration by patient-controlled analgesia (PCA) is the standard therapy for acute postoperative pain. Despite its utility in this setting, limitations of this modality do exist. Consequently, noninvasive PCA systems, including an iontophoretic transdermal system (ITS) with fentanyl hydrochloride, are under development to circumvent many of these limitations. This preprogrammed, self-contained, compact, needle-free system provides pain control superior to that of placebo and comparable to morphine PCA in the first 24 hours after major surgical procedures. The objectives of this article are to describe the method of transdermal iontophoretic medication administration and to review the literature pertaining to the fentanyl ITS.

Key words: iontophoresis, transdermal, fentanyl, opioid analgesics, patient-controlled analgesia, noninvasive method, postoperative pain, acute pain, breakthrough pain

INTRODUCTION

Opioids are the most commonly used analgesics for the management of moderate to severe acute pain in the postoperative setting¹; the most frequently used opioids are morphine and fentanyl.² Acute pain can be managed using a variety of modalities; however, since its introduction two decades ago,³ patient-controlled analgesia (PCA), which is usually administered via the intravenous (IV) or epidural route, has become the most common method of postoperative opioid delivery. Postoperative pain management has evolved over the last 20 years through the application of new knowledge and technology to existing opioids and the development of new methods of medication administration, such as PCA and spinal administration, rather than through the introduction of new medications.⁴

Although PCA with opioids has become one of the most effective techniques in the management of acute postoperative pain and a number of studies indicate that patients prefer this method of analgesic administration over more conventional methods (e.g., intramuscular [IM] injections on an

as-needed basis),⁵ a number of drawbacks are associated with its use. The administration of PCA requires equipment that is costly, cumbersome, and invasive. The typical PCA delivery system requires the technical expertise of involved nursing and pharmacy staff.⁶ Problems that compromise patient safety, such as programming errors, uncontrolled delivery of syringe contents, pump failures, syringe mix-ups, and inappropriate use of the system (e.g., patient tampering or family administration of doses by proxy), have all been reported.^{7,8} Failures of this delivery method secondary to IV line occlusions and catheter infiltration into the subcutaneous tissue are also possible.^{7,9,10} Consequently, noninvasive PCA systems that could circumvent many of these problems are under development, with the aims of maximizing efficacy and minimizing risks to the patient. If proven successful, an effective, noninvasive PCA system would be an attractive alternative for the control of postoperative pain.

Recently, a noninvasive patient-activated transdermal system that uses the iontophoretic drug delivery process known as E-TRANS[®] (ALZA Corporation, Mountain View, CA) to deliver fentanyl hydrochloride has been developed (fentanyl iontophoretic transdermal system [ITS]; IONSYS[™]; Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ). Formerly, the transdermal delivery of fentanyl has been limited to a commercially available patch formulation (Duragesic[®]; Janssen Pharmaceutica, L.P., Titusville, NJ); however, this transdermal therapeutic system (TTS) is contraindicated for use in the treatment of acute postoperative pain.¹¹ The features and uses of the fentanyl ITS are substantially different from those of the conventional TTS formulation. The objectives of this article are to describe the method of transdermal iontophoretic medication administration and to review the literature pertaining to the fentanyl ITS. To help achieve these objectives, a literature search of the MEDLINE database was carried out using the search terms "iontophoresis," "transdermal," "patient-controlled analgesia," "opioid," and "fentanyl." References were restricted to English-language articles published within the past 20 years (January 1986 to August 2006). Additional relevant literature was procured after searching the reference citations of retrieved articles.

TRANSDERMAL DRUG DELIVERY AND IONTOPHORESIS

Transdermal drug delivery holds significant potential for the noninvasive administration of therapeutic agents. It avoids the problems of first-pass metabolism and chemical degradation in the gastrointestinal tract and provides a simple method of continuous administration of medication.¹² In addition, the skin provides a large, accessible surface area for drug delivery. However, the principal disadvantage is that the composition and architecture of the skin render it a formidable barrier to chemical permeation.^{11,13-16} The major barrier to permeation is the uppermost of the five layers of the epidermis, the stratum corneum, which constitutes the rate-limiting layer for transdermal absorption of drugs.¹⁵ The physicochemical constraints of the stratum corneum (i.e., multiple layers of corneocytes embedded in lipid bilayers) severely limit the number and type of molecules that can be considered as realistic candidates for passive delivery via this route of administration.^{11,14,16}

In order for medications to penetrate the stratum corneum and reach the systemic circulation in clinically significant amounts, drugs need to be potent, have a low molecular weight (MW), and preferably be both lipophilic and ionized.¹²⁻¹⁵ The physicochemical and pharmacological properties of opioid analgesics (e.g., capable of eliciting a pharmacological effect at relatively low systemic concentrations, typically in the ng/ml range; MW in the range of 300 to 500 Da; and usually positively charged at physiological conditions) make these molecules candidates for transdermal delivery.¹⁴ However, the fundamental reason for there being so few transdermal opioids on the market is that the highly impermeable skin limits daily drug dosage, delivered from an acceptably sized patch, to about 10 mg.¹³

Fentanyl is a synthetic opioid that is widely used as both an analgesic and an anesthetic agent because of its rapid onset and short duration of action after parenteral administration.¹⁷ Several of fentanyl's characteristics make it the ideal opioid for transdermal delivery. Fentanyl is a very potent analgesic (100 to 500 times the analgesic efficacy of morphine per dose) with high affinity for the μ opioid receptor.¹⁴ Consequently, the dose needed to elicit a therapeutic response is on the order of magnitude of $\mu\text{g}/\text{kg}$ (rather than mg/kg), and the therapeutic levels necessary to produce analgesia (0.6 to 3 ng/ml) are much lower than those for other opioids, particularly morphine.^{14,18,19} Fentanyl has a low MW of 286 g/mol (morphine's MW is 337 g/mol)⁴ and is highly lipophilic, whereas morphine is a hydrophilic molecule. Fentanyl's lipid-soluble nature allows it to diffuse through the stratum corneum via the intercellular lipid medium.¹⁹ Fentanyl is positively charged at a physiological pH; 8.5 percent of fentanyl is un-ionized at a pH of 7.4, whereas morphine is 23 percent un-ionized at this pH level.^{14,19} Furthermore, fentanyl is subject to a considerable hepatic first-pass effect and variable metabolism, which preclude oral administration of the

drug.¹⁹ Unlike morphine, however, fentanyl does not have active metabolites that can accumulate over time.¹⁹ Thus, fentanyl is an ideal candidate for transdermal administration, and it was the first opioid analgesic commercially available for use via this route of administration.

A number of chemical and physical enhancement techniques have been developed in the hopes of increasing the range of medications available for transdermal delivery.¹⁴ Iontophoresis is a method of enhancing the transdermal administration of drugs across the skin by using an external electrical field.^{11,12,20} A number of comprehensive reviews have been written on this subject, and clinicians interested in this topic are encouraged to review these works.^{14,15,21,22} Briefly, the iontophoretic system consists of a skin delivery electrode, a skin current-returning electrode, and an electric power source. Iontophoresis functions via two main mechanisms: 1) the electrical repulsion of ionized drug from the delivery electrode, and 2) the electro-osmosis of drug via solvent flow into the stratum corneum (Figure 1).^{11,13,16,23} When an external electrical field is applied, the electrically charged components of the drug are propelled through the skin and into the systemic circulation.¹⁹ While iontophoresis substantially increases the penetration capacity of agents that are positively charged, lipophilic, and small in size,¹¹ this process is also capable of enhancing the delivery of both hydrophilic molecules and un-ionized moieties, including those that are not ideal candidates for this route of administration.^{14,15} For example, iontophoresis has been used to deliver clinically significant doses of morphine,²⁴ lidocaine,^{25,26} and corticosteroids to achieve analgesia.^{20,27}

For the advantages of iontophoresis to be realized in pain management, the delivery method must provide pain control that is comparable to that offered by current standard therapy.⁸ The efficiency and safety of this technique depend on several factors, such as current-wave form and electrode design.^{15,28} The factors affecting the delivery of fentanyl by iontophoresis have been investigated extensively, and it is recognized that delivery is affected by the physicochemical nature of the drug (e.g., molecular size) and its solution (e.g., pH, concentration) and the voltage, duration, and nature of the current.^{17,28-32}

PHARMACOKINETICS OF TRANSDERMAL FENTANYL DELIVERY

The fentanyl ITS is differentiated from the TTS formulation by its pharmacokinetics. There have been several reports in the literature describing the transdermal delivery of fentanyl via iontophoresis both *in vitro* and *in vivo*.^{17,29,33-39} Testing in healthy volunteers has indicated that the fentanyl ITS rapidly and consistently delivers calibrated, clinically significant doses of fentanyl into the systemic circulation.^{17,35} Patient characteristics such as age, gender, ethnicity, or body weight have been shown to have no significant pharmacokinetic effect.³⁹ Studies

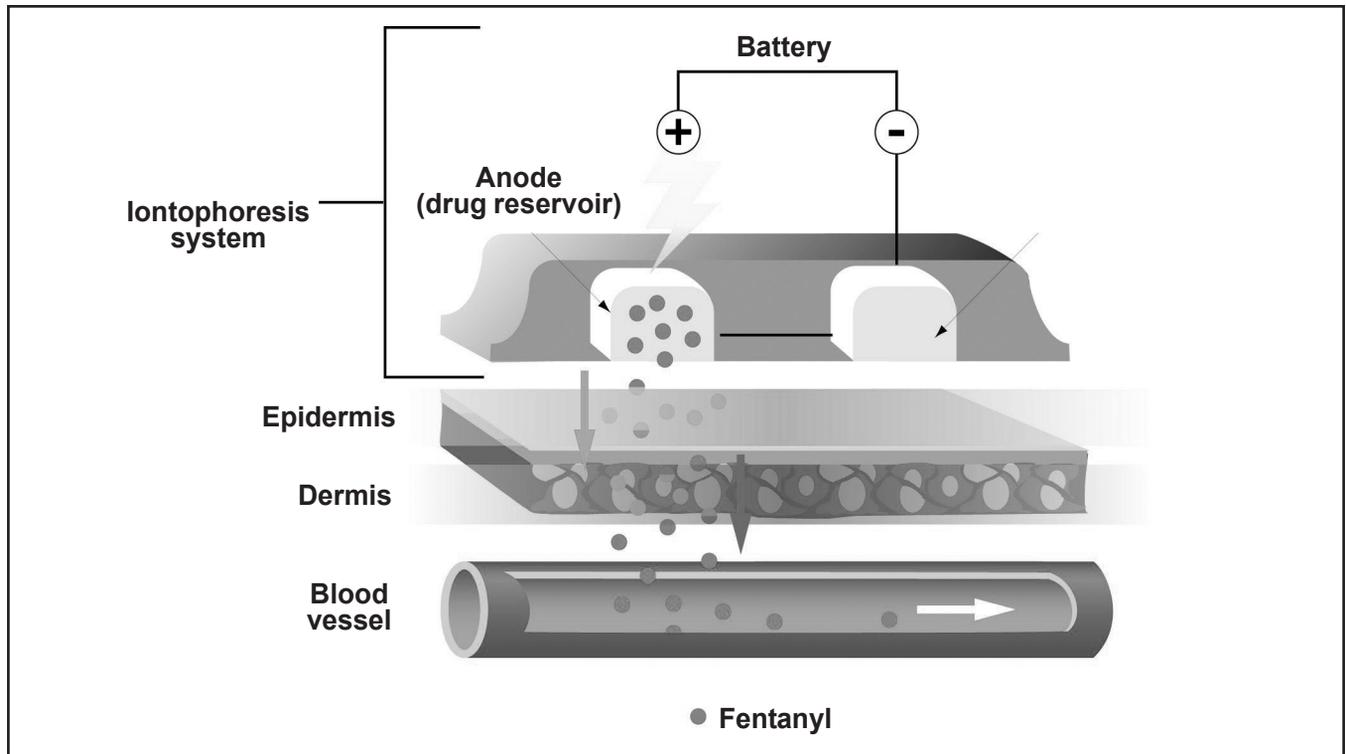


Figure 1. Schematic diagram of transdermal iontophoretic delivery of fentanyl. Reprinted with permission from Ortho-McNeil and Chelly JE.²³

have also demonstrated that the pharmacokinetics of fentanyl delivered by the ITS remain consistent over multiple-day administration periods at the same level of opioid consumption ($40 \mu\text{g}$)³⁸ and that the amount of drug absorbed from the system is independent of dosing frequency.³⁷ However, the amount of drug absorbed from the fentanyl ITS is proportional to the magnitude of the current applied to the system,¹⁷ with a $170 \mu\text{A}$ current/ 2.75 cm^2 delivering a nominal $40 \mu\text{g}$ dose of fentanyl.³⁸ It appears that a threshold current density ($\mu\text{A}/\text{cm}^2$) is required for a linear relation between current and amount absorbed. For fentanyl, this threshold current density seems to be about $75 \mu\text{A}/\text{cm}^2$ or greater.¹⁷ Thus, one may surmise that the dose of fentanyl administered by iontophoresis can be adjusted by changing the magnitude of the current. In fact, 24-hour continuous and on-demand drug delivery via iontophoresis is feasible.¹⁷ This is in contrast with the conventional fentanyl TTS, which has the advantage of a stable pharmacokinetic profile that mimics a continuous parenteral infusion for periods of between 48 and 72 hours with repeated dosing; however, this passive transdermal formulation does not afford the same degree of dose adjustment flexibility.

The TTS formulation of fentanyl is designed to enable consistent, continuous, passive absorption of fentanyl for the duration of the patch's application. This formulation uses a rate-controlling membrane permeation model and the principle of a concentration gradient for passive diffusion of fentanyl across the skin. After application of the first TTS, the

opioid is absorbed through the skin, and a depot of fentanyl concentrates in the upper skin layers. The skin depot needs to be reasonably filled before significant vascular absorption will occur.¹⁹ Thereafter, fentanyl becomes available to the systemic circulation, and it takes several hours' latency before the clinical effects of fentanyl can be observed.⁴ Specifically, fentanyl concentrations are not measurable until at least two hours after application of a 75 or $100 \mu\text{g}/\text{h}$ TTS^{40,41}; plasma concentrations of fentanyl peak at an average of 24 hours (range: 14 to 28 hours) after the patch is applied¹⁹ and approach steady state at approximately 72 hours postapplication.^{42,43} Conversely, the ITS uses iontophoresis to drive fentanyl across intact skin. Passive absorption of fentanyl from the ITS is minimal; in trials serum fentanyl levels were undetectable in patients when the system was applied without the activation of electrical current.³⁵ The mean amount of time between the activation of the fentanyl ITS and maximum serum concentration has been shown to be slightly longer than that seen with IV fentanyl administration over the same duration; however, the increase in concentration after termination of the ITS dose is small.^{11,38}

The presence of a fentanyl skin depot also has implications for the drug's duration of activity and elimination. Upon inactivation or removal of the fentanyl ITS, the rapid decline in serum fentanyl concentrations that occurs is similar to the decrease in serum fentanyl concentrations following the cessation of IV fentanyl treatment,^{17,36} suggesting that a subcutaneous depot or "reservoir effect" with the fentanyl ITS is minimal. In contrast,

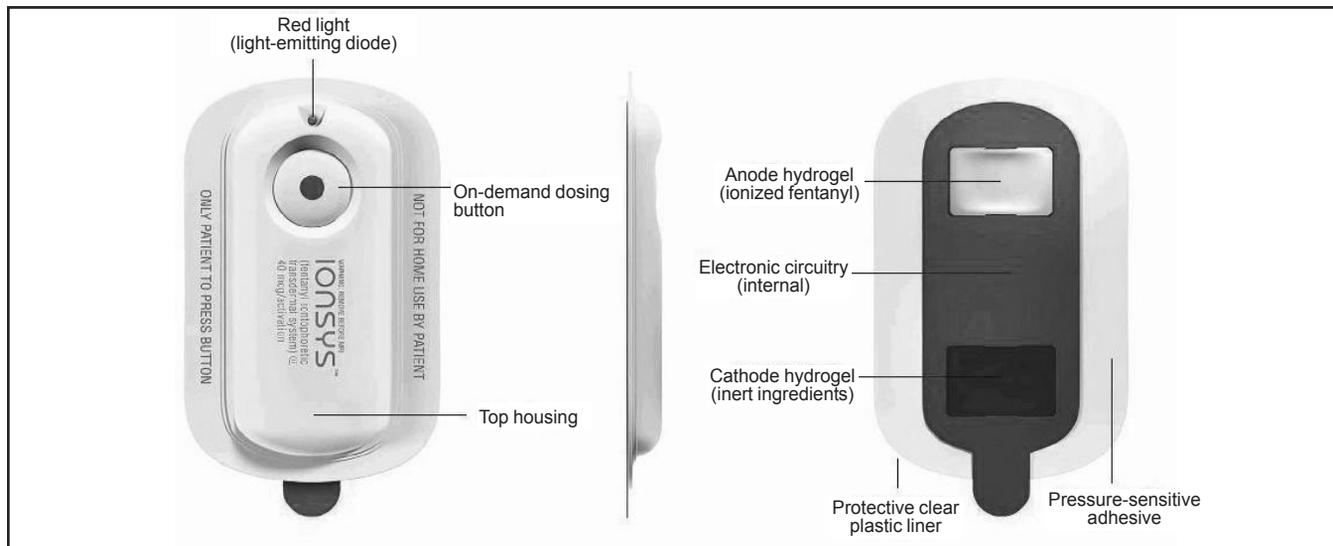


Figure 2. The fentanyl ITS (IONSYS™). The system is composed of a plastic top housing that contains a 3V lithium battery and electronics and a bottom housing containing two hydrogel reservoirs and a polyisobutylene skin adhesive. The anode hydrogel, which is located under the dosing button, contains fentanyl along with inactive ingredients; the cathode contains only inactive ingredients. The unit weighs 15 g and is 3.3 in long, 1.9 in wide, and 0.39 in high.⁵⁰ Reprinted with permission from Ortho-McNeil.

the prolonged terminal half-life of fentanyl after removal of the TTS is due to the slow, continued absorption of fentanyl from its cutaneous depot,^{40,44} as the amount of fentanyl remaining within the skin depot after removal of the patch is substantial.¹⁹ For example, at the end of a 24-hour period of use with the 100 µg/h TTS, 1.07 ± 0.43 mg of fentanyl, or approximately 30 percent of the total dose delivered, remains deposited in the skin.^{19,44} These differences in fentanyl absorption and elimination make the ITS better suited for the control of acute pain, such as in the post-operative setting, and the TTS formulation of fentanyl more appropriate for use in patients with chronic pain, such as those suffering from cancer-related pain.⁴⁵ Collectively, these pharmacokinetic data suggest that iontophoresis may enable transdermal administration of fentanyl with a rapid achievement of steady state and the ability to vary delivery rate. This capability would potentially be beneficial for the management of acute pain and breakthrough pain.¹²

DOSING AND ADMINISTRATION

The safety and efficacy of IV fentanyl PCA has been demonstrated with doses ranging from 10 to 60 µg using lockout intervals ranging from one to 10 minutes.⁴⁶⁻⁴⁹ The fentanyl ITS is preprogrammed to deliver a 40 µg dose over a 10-minute period.⁵⁰ The 40 µg dose was selected based on the results of the dose-finding study by Camu et al.,⁵¹ in which use of a 40 µg on-demand dose yielded an optimal profile of pain relief and safety compared with a 20 or 60 µg on-demand dose of fentanyl. A key objective in the optimization of an iontophoretic system is to maximize delivery while minimizing the level of the current¹⁴; the

density of the current (62 µA/cm²) provided by the fentanyl ITS is generally imperceptible to the patient.^{38,50}

In order for the electronic circuit for drug delivery to be complete, the system must be attached to the patient. The fentanyl ITS has an adhesive backing and is placed either on the outer upper arm or on the chest (Figure 2). The device should be applied to clean, dry, intact, nonirritated skin. Other application sites, such as the legs or abdomen, have not been studied; therefore, application to such sites is not recommended.⁵⁰ Drug delivery begins when the electrical field is activated by double-clicking the dose-activation button.⁸ In other words, absorption of clinically significant levels of drug occurs only after the patient activates the system.¹¹ The fentanyl ITS provides an audible tone (beep) and visual alert (red light from a light-emitting diode [LED]) to indicate the start of delivery of each dose; the red LED remains on throughout the dosing period.⁸ A system-initiated lockout prevents the patient from activating the system for additional drug during the 10-minute delivery period; this period is preprogrammed by the manufacturer, and fentanyl administration can not be interrupted, accelerated, or extended beyond this interval. Patients can initiate up to six doses an hour for up to 24 hours from the time the first dose was initiated or up to a maximum of 80 doses, whichever occurs first. If a treatment duration of longer than 24 hours (or 80 doses) is required, a new fentanyl ITS should be applied to a different application site.⁵⁰ After each dose is delivered, the LED turns off momentarily and then flashes to indicate the cumulative number of doses the patient has received, with each flash signifying delivery of a range of five doses (one flash = one to five doses delivered, two flashes = six to 10 doses, and so on, up to a maximum of 16 flashes [80 doses]).^{8,50}

Table 1. Summary of clinical trials evaluating the efficacy of fentanyl ITS

Reference	Treatment group	Dose	n	Study duration (h)	Primary efficacy endpoint	p value	Secondary efficacy endpoints					
							Mean pain intensity*	p value	PGA†	p value	IGA†	p value
Chelly 2004 ⁶	Fentanyl ITS	40 µg	142	24	25.4 percent	0.049	30.9 ± 2.4	0.047	3.0	0.047	3.1	0.007
	Placebo	–	47		40.4 percent		40.8 ± 4.6		2.6		2.6	
Viscusi 2006 ⁵²	Fentanyl ITS	40 µg	244	24	28.7 percent	< 0.0001	3.5 ± 0.16	< 0.0001	73.4 percent	< 0.0001	72.1 percent	< 0.0001
	Placebo	–	240		60.0 percent		5.4 ± 0.17		45.9 percent		46.6 percent	
Viscusi 2004 ⁸	Fentanyl ITS	40 µg	316	72	73.7 percent [§]	0.36	32.7	0.45	§		N/A	
	Morphine IV PCA	1 mg [‡]	320		76.9 percent [§]		31.1					

Abbreviations: IGA: investigator global assessment; ITS: iontophoretic transdermal system; IV: intravenous; N/A: not applicable; PCA: patient-controlled analgesia; PGA: patient global assessment. * Reported as mean last pain intensity recorded during the first 24 hours ± SEM. † In the study by Chelly et al.,⁶ PGA and IGA were rated on an ordinal scale, whereas in the trials performed by Viscusi et al.^{8,52} these measures were categorized on a nominal scale. The percentage of the latter reflects the proportion of patients and investigators, respectively, who considered the treatment a good or excellent method of pain control. ‡ The dose of morphine was a 1 mg bolus with a five-minute lockout interval. § Unlike in the placebo-controlled trials,^{6,52} the primary efficacy endpoint in this study was the PGA of method of pain control during the first 24-hour treatment period (combined rating of good and excellent). || Refers to the mean of the last recorded VAS within the first 24 hours (not 72 hours).

The audible and visual signals afforded by the fentanyl ITS provide information on system function and dosing similar to that of standard IV PCA,⁸ with the exception of cumulative dose approximation. For example, each system can be tested to ensure that it is operational while still in the pouch by locating the on-demand button through the foil packaging and pressing it twice. An audible beep will indicate that the system has been activated, and it will be followed by a series of beeps indicating that no dose was delivered. Testing the system in this manner does not initiate the 24-hour, 80-dose active delivery period, since no dose was delivered. Pressing the on-demand button once during or prior to drug delivery displays the approximate number of doses administered.⁵⁰ Alerts for nonfunctioning conditions are a short series of beeps (indicating decreased fentanyl delivery [e.g., poor skin contact] and that the fentanyl ITS should be restarted) and continuous beeping (indicating the system has shut down [e.g., low battery] and should be removed).

EFFICACY AND SAFETY

There are few published data on the clinical use of opioids delivered via iontophoresis, but the delivery of fentanyl via this mechanism has been investigated more extensively than that of other opioids.¹² Fentanyl ITS has been evaluated for the management of postoperative analgesia after abdominal, orthopedic, and thoracic surgery.^{6,8,52} The results of the

studies investigating the efficacy and safety of the fentanyl ITS are summarized in Tables 1 and 2, respectively.

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of the fentanyl ITS for the management of the first 24 hours of postoperative pain.⁶ The primary efficacy endpoint was the percentage of patients withdrawn from the study because of inadequate analgesia after completing at least three hours of treatment. Of the 189 patients considered evaluable for efficacy, 25 percent of patients in the fentanyl ITS 40 µg group withdrew because of inadequate analgesia, as compared with 40 percent of the placebo group (p = 0.049). Secondary efficacy endpoints included the last available mean pain intensity (measured using an ungraded visual analogue scale [VAS] that ranged from no pain [0 mm] to the worst possible pain [100 mm]) and patient and investigator global assessments (PGA and IGA, respectively) of the method of pain control at the end of the 24-hour study period or at the time of withdrawal (measured via a categorical scale with assigned values [1 = poor, 2 = fair, 3 = good, 4 = excellent]). The estimated number of treatment doses used by a patient, the number of patients requiring rescue medications during the first three hours, and the total amount of rescue medication administered were also recorded. Patients in the fentanyl group used a mean of 31 on-demand doses, whereas the placebo group used a mean of 27 doses (p value not reported). During the first three hours, 48 percent of the fentanyl group and 55 percent of the placebo group required rescue

medication ($p = 0.377$); the mean amount of IV fentanyl rescue medication given to each group was 99.6 μg and 95.4 μg , respectively (p value not reported). This study showed that the fentanyl ITS provided significantly better pain control than placebo for up to 24 hours after major surgery, as assessed by the primary efficacy endpoint of withdrawal secondary to inadequate analgesia; however, the difference between groups was marginal.

The findings by Chelly et al.⁶ were not as robust as would be expected in a placebo-controlled efficacy trial of opioid therapy. Several limitations were present in this study, including the lack of control for pain intensity at study entry and the randomization scheme used. These issues most likely contributed to the disappointing results seen. More specifically, approximately 19 percent of patients in the fentanyl group entered the study with a VAS pain score of ≥ 75 mm (indicative of severe pain), and the 3:1 fentanyl-to-placebo assignment disproportionately enrolled more patients with high baseline pain scores in the active treatment group, potentially underestimating fentanyl's overall efficacy.⁶ In order to address these limitations, Viscusi et al.⁵² employed a similar study design to compare the safety and efficacy of the fentanyl ITS with placebo for the management of moderate to severe postoperative pain. The primary difference between the studies conducted by Chelly et al.⁶ and Viscusi et al.⁵² was that patients included in the latter study were initially titrated to comfort with IV opioids (VAS score of < 5 as measured on an 11-point VAS with 0 denoting no pain and 10 the worst possible pain) prior to the application of the fentanyl ITS; in addition, a 1:1 randomization scheme was used. As in the study by Chelly et al.,⁶ the primary efficacy endpoint was the percentage of patients who discontinued participation in the study because of inadequate analgesia during the 24-hour treatment period. The investigators found that fewer patients using the fentanyl ITS discontinued therapy because of inadequate analgesia compared with the placebo group (29 percent versus 60 percent; $p < 0.0001$); also, a significantly larger proportion of patients receiving placebo discontinued the study for any reason (36.9 percent versus 68.3 percent; $p < 0.001$). Secondary efficacy endpoints included mean last pain intensity scores and PGA and IGA scores; global assessments of the method of pain control were categorically rated (poor, fair, good, or excellent). The estimated number of doses used by a patient and the proportion of patients requiring rescue medications during the first three hours were also recorded. At each measured time point, patients using the placebo system activated more doses per hour than patients receiving the active treatment (data not reported). A significantly larger percentage of patients receiving placebo required rescue medication in the first three hours of the study than patients receiving the active treatment (57.5 percent versus 45.5 percent, respectively; $p = 0.008$). These findings are more robust than the results from the earlier multicenter clinical trial by Chelly et

al.⁶; a 31 percent treatment difference was observed between groups who withdrew because of inadequate analgesia in the Viscusi et al.⁵² study, compared to the marginal 15 percent in the study by Chelly et al.⁶

In a multicenter, randomized, unblinded, active-control study, Viscusi et al.⁸ established that the fentanyl ITS is equivalent to a standard morphine IV PCA regimen in postoperative pain management. The primary efficacy endpoint was PGA at 24 hours, which was measured as a categorical variable of the method of pain control (poor, fair, good, or excellent). Ratings of good or excellent (categorized as success) were given by 73.7 percent and 76.9 percent of patients in the treatment groups, respectively; treatment difference was -3.2 percent (95 percent confidence interval [CI]: -9.9 percent to 3.5 percent; $p = 0.36$). According to the investigators' definition of the primary endpoint, fentanyl ITS and morphine PCA were therapeutically equivalent (i.e., 95 percent CI of the difference in success rate fell within ± 10 percent, with $\alpha = 0.025$). Additional efficacy measures were the proportion of patients discontinuing the study because of inadequate analgesia or for any reason, patient-reported pain intensity scores on a 100 mm ungraded VAS (no pain = 0 mm, worst possible pain = 100 mm), PGA at 48 and 72 hours, and the proportion of patients requiring rescue medications during the first three hours. Withdrawals secondary to inadequate analgesia were fewer but not statistically significant in the morphine PCA group (10.3 percent) compared with the fentanyl ITS group (15.2 percent; $p = 0.07$). There also was no difference in the number of withdrawals due to adverse events (5.9 percent versus 6.0 percent, respectively; $p = 0.97$). With continued treatment for up to 48 to 72 hours, more than 80 percent of patients in each treatment group rated the pain control as good or excellent. The proportion of patients who received supplemental IV opioids within the first three hours after treatment initiation was also similar for both treatment groups (fentanyl, 22.8 percent, versus morphine, 27.2 percent; $p = 0.20$).

Overall, patients included in these studies were predominantly female (69 to 74 percent), white (73 to 84 percent), and approximately 50 years of age, and the majority had an American Society of Anesthesiologists physical status of II (mild to moderate disturbance). Limitations of the studies with regard to assessment of the efficacy of this fentanyl ITS were related to the study design and the system itself. The first such limitation is attributable to the comparison with placebo^{6,52} and disallowing patients to receive additional analgesics after a set period of time (e.g., three hours).^{6,8,52} Current approaches for acute pain management use adjuvant analgesics such as regional blocks or systemic nonsteroidal anti-inflammatory drugs in combination with PCA⁵³; such treatment modalities were not allowed in these studies. Therefore, the external validity of these studies is somewhat suspect, as these exclusions do not mirror the "real world" of acute pain management.⁵⁰ Future studies of the fentanyl ITS will need to address its use in a multimodal analgesic

Table 2. Most common treatment-related adverse events reported in clinical trials of fentanyl ITS (≥ 2 percent of patients)*

Adverse event	Treatment group I ⁶		Treatment group II ⁵²		Treatment group III ⁸	
	Fentanyl ITS (n = 154)	Placebo (n = 51)	Fentanyl ITS (n = 244)	Placebo (n = 240)	Fentanyl ITS (n = 316)	Morphine IV PCA (n = 320)
Nausea	48 (31.2)	13 (25.5)	65 (26.6)	35 (14.6)	129 (40.8)	147 (45.9)
Vomiting	11 (7.1)	0 (0)	10 (4.1)	10 (4.2)	31 (9.8)	27 (8.4)
Headache	10 (6.5)	4 (7.8)	10 (4.1)	8 (3.3)	36 (11.4)	24 (7.5)
Pruritus (general)	18 (11.7)	3 (5.9)	8 (3.3)	1 (0.4)	26 (8.2)	(0)
Application site reactions (pruritus, vesicles, other)	8 (5.2)	5 (9.9)	11 (4.5)	3 (1.3)	20 (6.3)	40 (12.5)
Constipation	NR	NR	NR	NR	12 (3.8)	7 (2.2)
Hypoxemia	2 (1.3)	0 (0)	NR	NR	12 (3.8)	7 (2.2)
Fever	NR	NR	6 (2.5)	4 (1.7)	11 (3.5)	13 (4.1)
Dizziness	1 (0.6)	1 (2.0)	6 (2.5)	2 (0.8)	6 (1.9)	12 (3.8)
Somnolence	NR	NR	NR	NR	6 (1.9)	7 (2.2)
Anxiety	NR	NR	NR	NR	4 (1.3)	9 (2.8)
Gastrointestinal disorder	2 (1.3) [†]	1 (2.0) [†]	2 (0.8) [‡]	0 (0) [‡]	3 (0.9) [‡]	2 (0.6) [‡]
Urinary retention	1 (0.6)	1 (2.0)	NR	NR	5 (1.6)	2 (0.6)
Hypertension	0 (0)	1 (2.0)	NR	NR	NR	NR
Bradycardia	0 (0)	1 (2.0)	NR	NR	NR	NR
Insomnia	NR	NR	6 (2.5)	8 (3.3)	NR	NR

Abbreviations: ITS: iontophoretic transdermal system; IV: intravenous; NR: not reported; PCA: patient-controlled analgesia.

* Values are given as n (percent). [†] Not specified. [‡] Ileus.

setting.⁸ Because the fentanyl ITS is programmed to only indicate the approximate number of doses delivered, whereas PCA pumps indicate the precise number of doses delivered, the patient-administered dose is estimated. In all three of the efficacy trials, the total fentanyl dose administered via the ITS was estimated as five times the number of displayed light flashes minus two to obtain the midrange dose number; as mentioned, each flash represents the delivery of one to five doses, corresponding to the delivery of 40 to 200 $\mu\text{g}/\text{h}$ of fentanyl. In practice, individual patients may require varying amounts of drug based on differences in their pain perception, opioid tolerance, or weight, and therapy is frequently adjusted based upon previous opioid dose. However, a five-fold difference in estimated dose may result in either under- or overestimation of true opioid requirements, potentially delaying subsequent achievement of adequate analgesia or resulting in overdose if supplemental or alternative opioid analgesics are used in conjunction with or to replace (respectively) the fentanyl ITS. Therefore, it is imperative that

patients are titrated to an acceptable level of analgesia before initiating treatment with the fentanyl ITS. Patients should be evaluated frequently to ensure that they are receiving adequate analgesia, and subsequent adjustments in the patient's pain regimen should be made by medical personnel with expertise in pain management.

The most frequent treatment-related adverse events reported in clinical studies of the fentanyl ITS are summarized in Table 2. In general, most adverse events viewed as probably related to the fentanyl ITS were judged to be mild to moderate in severity and were either opioid-related (e.g., constipation, somnolence) or local effects (e.g., pruritus),^{6,8,52} all of which are commonly experienced by patients receiving opioid analgesia and by those in the immediate postoperative period.⁵⁴ Nausea was the most commonly reported systemic adverse event associated with treatment, ranging in incidence from approximately 30 percent to 40 percent. The most commonly reported application site reaction was erythema, which was believed to be

related to the delivery mode itself and not to fentanyl. Scheduled skin evaluations after system removal revealed erythema in 54, 45, and 25 percent of patients receiving active treatment in trials performed by Viscusi et al.,⁸ Chelly et al.,⁶ and Viscusi et al.,⁵² respectively, although, on the whole, application site reactions were reported in less than 10 percent of all patients. Most erythema was mild and self-limiting and resolved without treatment.^{6,8,52} In all three clinical trials of the fentanyl ITS, respiratory function was the primary measure of systemic safety, and clinically relevant respiratory depression (CRRD) was defined as the simultaneous occurrence of bradypnea (respiratory rate < 8 breaths/min) and excessive sedation (patient not easily aroused).^{6,8,52} Importantly, no patient who received this therapy experienced CRRD.

The biophysical effects of iontophoresis itself have been extensively reviewed by Jadoul et al.⁵⁵ and Curdy et al.¹⁶ Briefly, skin appendages, which include sweat glands and hair follicles, are postulated to be major pathways of drug transport during iontophoresis.^{15,56} There is concern about iontophoresis causing damage to growing hair and other possible irreversible changes to the skin at clinically acceptable current densities.⁵⁷ However, evidence from studies of iontophoretic delivery in both hairless mice and excised human skin suggests a much larger contribution by sweat glands and ducts, as opposed to hair follicles, in the pathway of electric current.⁵⁶⁻⁶⁰ In fact, tap-water iontophoresis is one of the most popular treatments for hyperhidrosis (or hyperhidrosis), defined as excessive sweating of the hands and feet.^{61,62} Overall, however, the evidence for the dominant current path via iontophoresis is conflicting.^{63,64} To date, there have been no reports of hair loss or permanent skin damage in randomized, controlled trials of transdermal iontophoretic PCA with fentanyl.

THERAPEUTIC USES

Iontophoresis as a process of transdermal drug delivery has applications in pain management, allowing noninvasive administration of opioid analgesics.¹⁴ As mentioned, the amount of drug delivered by the device to the patient is linearly related to the magnitude of the electric current applied to the system.³⁸ Therefore, appropriate modulation of the current's profile means that iontophoresis can be used to deliver analgesics via the transdermal route to provide relief in response to acute pain episodes as well as to alleviate chronic pain. Furthermore, in addition to providing a mechanism to deliver drugs to achieve systemic pain relief, iontophoresis can be used as an administration modality for local analgesics to provide local pain relief or local anesthesia prior to minor surgical procedures.¹⁴

The effectiveness of transdermal fentanyl administration was first demonstrated with acute postoperative pain. Peng and Sandler¹⁹ extensively reviewed the literature related to the use of the fentanyl TTS as an analgesic in

the postoperative period. The results of their review indicate that because of the slow attainment of an analgesic plasma concentration, the inability to rapidly adjust the dose, and the relatively short duration of postoperative pain, the fentanyl TTS formulation should not be used for management of acute pain. Furthermore, a high incidence of CRRD associated with the conventional TTS was also reported in this and other reviews of the literature^{4,19,65}; such use is now contraindicated. On the other hand, clinical trials have shown the fentanyl ITS to be superior to placebo and comparable to morphine PCA in terms of both efficacy and safety for the treatment of acute postoperative pain. It is for this reason that the US Food and Drug Administration approved fentanyl ITS (May 22, 2006) for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization; commercial availability is not expected until 2007.

It is possible that the fentanyl ITS may have therapeutic applications outside of postoperative pain management, such as for the management of breakthrough pain experienced by cancer patients. Those who have pain that requires the long-term administration of opioids (such as patients with cancer pain or chronic nonmalignant pain) benefit from constant, time-contingent (e.g., around-the-clock) opioid administration. In addition, these patients frequently require the rapid administration of potent immediate-release opioids for the management of breakthrough and incident pain. As stated, the fentanyl TTS is a noninvasive, passive delivery system for time-contingent analgesic therapy. Numerous studies have demonstrated the effectiveness of the fentanyl TTS in the treatment of chronic cancer and noncancer pain.⁶⁶⁻⁷⁴ This formulation's prolonged 72-hour duration of therapy is ideal for chronic pain states in which the patient's pain is fairly stable but displays slow onset and offset not suitable for acute pain management.⁷⁵ Iontophoresis may allow rapid administration of additional amounts of fentanyl for the management of incident and breakthrough pain, and iontophoresis, as a mode of drug delivery, provides a level of flexibility in adjusting the amount of fentanyl delivered.^{4,29} However, as previously mentioned, the fentanyl ITS is preprogrammed to deliver a 40 µg dose of fentanyl upon patient demand, and the dose delivered by the system can not be adjusted. The use of the fentanyl ITS for these and other related indications has yet to be investigated in controlled clinical trials, so use of the fentanyl ITS for any off-label indication is not recommended.

SUMMARY

In order for an iontophoretic product to find a place in a clinician's armamentarium, this technology must provide added value over existing administration methods.¹⁴ Aside from the pharmacokinetic and pharmacodynamic benefits of fentanyl itself, there are several potential

advantages to the fentanyl ITS. The system provides pain control comparable to that offered by a standard regimen of morphine PCA, without the pump apparatus, IV lines, tubing, and other equipment required for PCA administration.⁸ Because the fentanyl ITS is preprogrammed and relatively easy to operate, there is a low risk of dosing errors and potentially fewer administrative, technical, and clinical resources required to operate the system. Also, the self-contained transdermal drug delivery system is convenient and may aid patient mobility, especially after major surgery. Furthermore, in clinical trials most patients were very satisfied with the pain control provided by the fentanyl ITS, and most patients characterized the system as very convenient and very easy to use.^{8,52}

Use of the fentanyl ITS also has a number of associated limitations. Appropriate selection of patients is necessary for safe and effective use of the system. Current practice dictates that patients using PCA should be awake, alert, and able to understand how to use the device; these same requirements apply in use of the fentanyl ITS.⁵⁰ Patients unable to operate the system because of deficiencies in upper extremity mobility or comprehension would not be appropriate candidates for either standard opioid PCA or the fentanyl ITS.⁷⁶ Although the process of iontophoresis affords the ability to titrate medication dosage, thus making continuous iontophoretic delivery of fentanyl feasible,¹⁷ fentanyl ITS is not a continuous drug delivery system and therefore would not be appropriate as monotherapy for the management of chronic pain. The rationale for the development of the current, intermittent fentanyl ITS was that previous studies indicated that a continuous basal infusion does not enhance efficacy during acute use in the postoperative setting.^{7,19} Moreover, this system is intentionally not designed to treat the intense levels of pain immediately following surgery; rather, it is meant to deliver small, frequent doses of fentanyl to maintain analgesia once initial pain control has been established, typically with parenteral opioids. This is consistent with the manner in which PCA is currently used in the clinical postoperative setting.⁵² The fentanyl ITS may not be appropriate for opioid-tolerant patients, whose opioid dose requirement may be higher than that provided by the system.⁸ Future research and development efforts may lead to the availability of varying dosage strengths that would allow for even more versatility for this product and potentially result in wider clinical application.⁴⁵

Additional concerns regarding the fentanyl ITS involve the high incidence of application site reactions and the paucity of pharmacoeconomic data. The skin irritation associated with iontophoresis in general has been addressed by several studies, and it is an issue preventing wide application of this technology. However, the use of ITS in combination with other enhancement techniques (e.g., electroporation, sonophoresis) may result in lower current levels being able to deliver therapeutically effective

amounts of medication, and this may dramatically reduce the skin irritation problem.¹⁵ In terms of cost, there have been no studies to date evaluating the cost effectiveness of the fentanyl ITS. Evidence suggests that postoperative pain (in particular) continues to be treated inadequately and that this is one reason that many patients postpone elective surgery.⁷⁷⁻⁸² Inadequate pain control in the postoperative period not only contributes to patient discomfort but also may reduce patient satisfaction with hospital care, prolong and complicate a patient's recovery, and increase healthcare costs.^{45,76,78,83,84} In contrast, effective pain management may lead to increased patient satisfaction, a less complicated postoperative course including earlier hospital discharge, decreased resource utilization, and lower direct and indirect costs.^{85,86} Effective analgesia may also prevent the development of chronic pain syndromes, which are extremely expensive and difficult to manage.⁷⁷ A cost comparison between standard IV PCA and the fentanyl ITS is warranted.

In conclusion, the application of new knowledge and technology to existing opioids such as fentanyl provides physicians and healthcare teams with new treatment options in pain management. Iontophoresis is one method of enhancing transdermal drug delivery that shows considerable promise in pain medicine. The fentanyl ITS addresses some of the limitations of traditional PCA administration while still providing patients with personal control over their pain management. The on-demand dosing and pharmacokinetics of this system differentiate it from the fentanyl TTS, which was designed for the management of chronic pain. The fentanyl ITS has been demonstrated to be effective for the management of acute postoperative pain, but its use may not be limited to this area. Well-designed, randomized, controlled studies should examine the safety and efficacy of the fentanyl ITS for pain management in additional settings and indications; these include ambulatory surgery, labor and delivery, adjunct therapy for regional anesthesia, and moderate to severe cancer-related pain, among others. In addition, a comparative cost-benefit analysis incorporating the potential for improved safety and decreased demand for resources would provide further insights into the potential economic advantages of the iontophoretic fentanyl ITS.

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