Fentanyl HCl iontophoretic transdermal system (ITS): clinical application of iontophoretic technology in the management of acute postoperative pain

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The fentanyl HCl iontophoretic transdermal system (fentanyl ITS) is a novel patient-controlled analgesia (PCA) system that has been approved in the USA and Europe for the management of acute, moderate-to-severe postoperative pain. This system extends the applicability of transdermal drug delivery to acute pain management, allowing patients to self-administer pre-programmed doses of fentanyl non-invasively through the use of iontophoretic technology. Iontophoresis is the process by which an electric current is used to drive ionized drug molecules across the skin and into the systemic circulation. Results of a recent US clinical trial found the fentanyl ITS to provide pain control equivalent to a standard regimen of morphine i.v. PCA, with a similar incidence of opioid-related adverse events. The fentanyl ITS may offer a number of clinical advantages over existing PCA modalities. Its method of drug delivery avoids the risk of complications from needle-related injuries and infection, and its pre-programmed electronics eliminate the potential for manual programming errors and excessive dosing. In addition, the compact size of the system could enable greater patient mobility following surgery. The fentanyl ITS has the potential to become a valuable option in the management of acute postoperative pain.

Keywords: analgesia, patient-controlled; analgesics opioid, fentanyl; iontophoresis, transdermal; pain, postoperative

Despite the potential benefits to patient health that can result from effective pain management, survey results continue to indicate that acute postoperative pain remains inadequately managed worldwide. The development of novel analgesics and advanced analgesic techniques has the potential to improve current strategies for postoperative pain management. Transdermal drug delivery is a promising, non-invasive strategy for the safe and effective administration of pain medication. Conventional transdermal analgesic modalities (e.g. drug-infused patches and topical creams) utilize passive diffusion to provide effective relief from chronic or localized pain. Transdermal drug absorption occurs slowly by passive diffusion, and conventional transdermal devices are unable to administer individual, on-demand doses. Therefore, these strategies are inappropriate for acute pain management. Technological advances have led to the development of an active transdermal fentanyl delivery system that uses the process of iontophoresis for the management of acute, moderate-to-severe postoperative pain. The fentanyl HCl iontophoretic transdermal system (fentanyl ITS; IONSYS™, Janssen-Cilag NV, Beerse, Belgium) significantly enhances the rate of transdermal fentanyl delivery relative to passive diffusion through the electro-repulsion of ionized drug molecules. The objective of this article is to review the characteristics and clinical effectiveness of the fentanyl ITS, describing its advanced approach to transdermal drug delivery and highlighting key findings from clinical studies.

Patient-controlled analgesia

Over the past two decades, the drive to improve the treatment of postoperative pain has led to the development of pain management guidelines and the institution of specialized acute pain teams in hospitals worldwide. In addition, the development of patient-controlled analgesia (PCA), particularly using the i.v. and extradural routes, has resulted in marked improvements in the management of acute postoperative pain. PCA allows patients to self-administer analgesics according to their personal requirements for pain relief. Consequently, patients can maintain a uniform level of analgesia and avoid...
potentially long delays in the administration of analgesics by busy hospital personnel.\textsuperscript{55}

Extradural analgesia [including patient-controlled extradural analgesia (PCEA)] and i.v. PCA are associated with more effective pain relief and higher levels of patient satisfaction compared with conventional parenteral analgesic modalities.\textsuperscript{5, 18, 58} However, several drawbacks associated with these techniques may limit the extent to which they improve postoperative pain management. Both methods of drug delivery are invasive, requiring a needle for administration. This requirement introduces the risks of needle-stick injury and infection to the patient and hospital personnel. Extradural administration is also associated with a risk of neurological injuries from needle trauma and a high rate of technical failures resulting from migration or dislodgement of the catheter.\textsuperscript{64} In addition, both strategies utilize a PCA pump that must be programmed by hospital personnel, and programming errors have resulted in the administration of improper doses, oversedation, and, in some cases, death.\textsuperscript{1, 34, 54}

**Transdermal drug delivery**

The transdermal route of analgesic delivery offers a number of advantages over existing strategies for the systemic administration of analgesics. The requirements for the use of needles and venous access are eliminated, making analgesic administration less invasive, simpler, and more convenient. Similar to parenteral routes, drug delivery via the transdermal route also by-passes first-pass hepatic metabolism and circumvents common barriers to the use of oral analgesics immediately following surgery, such as nausea and vomiting, and difficulty swallowing.

Drug transport across the skin can occur through hair follicles and sweat ducts, but the main route of diffusion is through the stratum corneum via a lipid-rich, intercellular pathway.\textsuperscript{9} However, the stratum corneum presents a significant challenge to passive transdermal drug delivery, and optimal analgesic agents must have certain characteristics, including a low molecular weight (<1000 g mol\textsuperscript{-1}), appropriate solubility in water and oil, an optimal partition coefficient between the membrane and the solution, and a low melting point.\textsuperscript{9, 45} The physical chemical characteristics of fentanyl make it optimal for transdermal administration. It has a low molecular weight of 286 g mol\textsuperscript{-1}, high lipophilicity (octanol–water partition coefficient of 717), and optimal skin flux (approximately 1000 times that of morphine).\textsuperscript{21}

Conventional strategies for transdermal fentanyl delivery, such as skin patches that contain a drug reservoir or are drug-infused, rely on the gradual penetration of skin by passive diffusion, which makes them appropriate for chronic pain relief. Transdermal fentanyl patches have also been evaluated for continuous fentanyl delivery in the management of acute pain following several surgery types, in which they have demonstrated a reduction in parenteral opioid use, compared with placebo.\textsuperscript{30, 31} However, passive transdermal fentanyl delivery results in the build-up of fentanyl in a skin depot, which results in prolonged fentanyl delivery after removal of the patch,\textsuperscript{52} along with an increased potential for respiratory depression when treating acute pain.\textsuperscript{21} Thus, passive transdermal fentanyl administration is currently contraindicated for acute postoperative pain management.\textsuperscript{27, 53} One approach to enhance the rate of drug penetration through the stratum corneum relative to passive diffusion and to provide more precise control over analgesic delivery is through the use of iontophoretic technology.\textsuperscript{28}

**Iontophoresis**

Iontophoresis uses a low-intensity electric current to transport ionized drug molecules actively across the skin and into the systemic circulation (Fig. 1). Electric current flows from the anode to the cathode, with the skin completing the circuit. Current flowing through an electrode in the drug-containing reservoir drives ionized drug molecules into the skin via both electro-repulsion of similarly charged molecules and bulk fluid flow resulting from electro-osmosis.\textsuperscript{9, 17, 40} The flow of electric current may also increase skin permeability, which is reversible and not indicative of skin damage.\textsuperscript{7} Iontophoresis has been shown to be well tolerated by the skin, and the sensations that occur as a result of current flow have typically been minor.\textsuperscript{17} Mild erythema has been reported in some patients in the area beneath the electrodes, although it has generally been mild and has resolved within 24 h.\textsuperscript{6}

Many variables influence the quantity of drug delivered by an iontophoretic system, including the surface area of skin in contact with the electrode compartment, duration and intensity of the electric current, and chemical properties of the drug and drug formulation. In general, greater efficiency of iontophoretic drug delivery occurs with low molecular weight compounds that are lipophilic and positively charged.\textsuperscript{28}

A wide variety of pharmaceuticals have been administered using iontophoresis, with varying degrees of success. Iontophoresis of lidocaine was found to provide effective dermal analgesia in patients receiving propofol injection\textsuperscript{46} and in patients undergoing spider vein cauterization\textsuperscript{11} or venipuncture,\textsuperscript{29, 44} and it was a superior dermal analgesic compared with topical lidocaine/prilocaine cream.\textsuperscript{26} Corticosteroids administered by this method have been shown to reduce symptoms of joint inflammation.\textsuperscript{10, 36} In a study of patients (N=199) with pain associated with medial or lateral epicondylitis, dexamethasone administered using iontophoresis significantly improved patient visual analogue scale (VAS) ratings, investigator’s global improvement scale ratings, and investigator-rated pain and tenderness scores 2 days post-treatment compared with placebo.\textsuperscript{30} These and other data have established the safety and efficacy of iontophoretic drug delivery previously, particularly for pain relief.

However, the number of opioids suitable for iontophoretic delivery is limited.\textsuperscript{21} Clinical studies have evaluated the
iontophoretic delivery of morphine, but its low lipid solubility hinders optimal skin penetration. Iontophoresis produced detectable serum levels of morphine after 5 min with maximum concentrations ranging from 11.4 to 19.8 mg litre\(^{-1}\). Iontophoretically delivered morphine also reduced patients’ need for pethidine by 43% following hip or knee replacement surgery compared with placebo. Serum morphine levels of treated patients in this study were 20–60 mg litre\(^{-1}\), and iontophoresis-related adverse events were minimal (three patients experienced minor skin irritation) and resolved within 72 h, suggesting that iontophoresis is a feasible modality for postoperative opioid analgesia. However, the physical chemical properties of morphine make it difficult to achieve the systemic levels necessary for adequate amelioration of moderate-to-severe acute pain using iontophoresis alone. In contrast, fentanyl is ideal for iontophoretic transdermal delivery, and studies have shown that it can be administered in clinically significant doses to reach circulating levels similar to those achieved by i.v. infusion using a low-intensity electric current. Iontophoresis offers precise control over the frequency of analgesic dosing using a non-invasive approach. Thus, iontophoresis enables the management of acute postoperative pain using the transdermal route. An iontophoretic transdermal fentanyl delivery system that has recently been developed for postoperative pain management and has been designed for PCA using the transdermal route is the fentanyl ITS.

The fentanyl HCl iontophoretic transdermal system

Description of the system

The fentanyl ITS is a needle-free, iontophoretic PCA system that has been approved in the United States and Europe for the management of acute, moderate-to-severe postoperative pain in hospitalized adult patients (Fig. 2). It may be applied to the patient’s chest or upper outer arm using an adhesive that covers the bottom of the drug component housing. The patient activates the system by pressing the recessed dosing button twice within 3 s. Activation produces a low-intensity electric current (170 \(\mu\)A) flow through the system. Positively charged fentanyl molecules within the...
anode hydrogel reservoir are then repelled from the positively charged anode surface and delivered transdermally into the systemic circulation. The fentanyl ITS delivers a pre-programmed 40 µg dose of fentanyl over a 10 min period. Additional dosing requests are prevented by the system during drug delivery, thus, patients may self-administer a maximum of six doses per hour. The fentanyl ITS functions for up to 24 h or a maximum of 80 doses (whichever occurs first), after which it shuts down automatically. The system may then be removed and discarded, and a new system may be applied to a different skin site if additional analgesia is required.

The entire system is compact and is self-contained within a compact plastic housing. The dosing status of the system is indicated by a small, light-emitting diode (LED) and audible beeps. Illumination of the red LED and a single beep indicate the beginning of each dose, and the LED remains on until delivery of a dose has completed. Between doses, the system automatically communicates the approximate number of doses delivered via a series of light flashes from the LED. The total dose count may also be displayed during drug delivery by pressing the dosing button once.

**Pharmacokinetics of transdermal fentanyl administration: passive vs active delivery**

A commercially available fentanyl patch uses transdermal fentanyl delivery for the effective management of chronic pain. The patch continuously delivers fentanyl through the skin via passive diffusion from a polymer matrix. Fentanyl delivery by the transdermal patch is characterized by a slow rate of drug absorption and sustained serum concentrations after patch removal, which is suitable for the management of chronic pain, but inappropriate for the management of acute pain.

Results from clinical studies have shown that iontophoretic drug administration using the fentanyl ITS enhances the rate of fentanyl absorption into the bloodstream relative to passive diffusion. Across studies, the mean time to maximum fentanyl serum concentration ($t_{\text{max}}$) was shown to range from 12 to 48 h using the fentanyl patch, depending upon both the delivery rate and the duration of administration. In a single study, iontophoretic delivery of fentanyl using the fentanyl ITS resulted in a $t_{\text{max}}$ of approximately 39 min after the completion of delivery of a single dose (Table 2). The decline in serum fentanyl concentrations following termination of treatment also occurs more rapidly with the fentanyl ITS than with the fentanyl patch. Results of a pharmacokinetic study showed that the mean serum terminal half-life ($t_{1/2}$) after cessation of fentanyl ITS treatment was 11.0 h, with a slope of the terminal serum concentration decline similar to that observed after i.v. fentanyl infusion. These data would appear to indicate that fentanyl does not accumulate in a skin depot during drug delivery by the fentanyl ITS. This is in contrast to the gradual release of fentanyl into the systemic

### Table 1 Comparison of mechanisms for transdermal analgesic administration.

<table>
<thead>
<tr>
<th>Mechanism of delivery</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Passive diffusion</td>
<td>No first-pass effect</td>
<td>Slow rate of analgesic absorption</td>
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<tr>
<td></td>
<td>Non-invasive</td>
<td>Cannot control dosing via PCA</td>
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<tr>
<td></td>
<td>Convenient to administer</td>
<td>Limitations to choice of analgesics</td>
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<tr>
<td></td>
<td>Ability to treat chronic pain (skin depot effect)</td>
<td>Inappropriate for patients with skin disorders</td>
</tr>
<tr>
<td>Iontophoresis</td>
<td>No first-pass effect</td>
<td>Limitations to choice of analgesics</td>
</tr>
<tr>
<td></td>
<td>Non-invasive</td>
<td>Inappropriate for patients with skin disorders</td>
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<td></td>
<td>Convenient to administer</td>
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<tr>
<td></td>
<td>Ability to treat acute pain (no skin depot effect)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid rate of analgesic absorption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid decline in serum fentanyl concentrations</td>
<td>Similar to that of i.v. fentanyl infusion</td>
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<tr>
<td></td>
<td>Can control dosing precisely via PCA</td>
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### Table 2 Comparison of pharmacokinetic parameters following i.v. or transdermal fentanyl delivery. ITS, iontophoretic transdermal system; $t_{\text{max}}$, time to peak serum concentration; $t_{1/2}$, serum terminal half-life.

<table>
<thead>
<tr>
<th>Method of fentanyl delivery</th>
<th>Mean $t_{\text{max}}$</th>
<th>Mean $t_{1/2}$</th>
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<tbody>
<tr>
<td>Passive transdermal delivery</td>
<td>12–48 h</td>
<td>13–25 h</td>
</tr>
<tr>
<td>I.V. infusion</td>
<td>35 min</td>
<td>13 h</td>
</tr>
<tr>
<td>Fentanyl ITS (iontophoresis)</td>
<td>39 min</td>
<td>11 h</td>
</tr>
</tbody>
</table>
circulation after cessation of treatment with the transdermal fentanyl patch.

Pharmacokinetic studies have found the serum $t_{1/2}$ of fentanyl to range from 13 to 25 h following removal of the transdermal patch. As the transdermal patch administers fentanyl continuously after application to the skin, it lacks the ability to deliver individual, on-demand doses. In contrast, the fentanyl ITS delivers controlled doses of fentanyl only after activation of its electronic circuitry; minimal passive diffusion of fentanyl was found to occur from an inactivated fentanyl ITS, resulting in clinically insignificant drug absorption into the serum. The 40 μg dose of fentanyl delivered by the fentanyl ITS was selected based on the results of a dose-finding study that evaluated three fentanyl doses (20, 40 and 60 μg), which found this dose to optimize analgesic efficacy with an acceptable side-effect profile. The higher dose (60 μg) resulted in an increase in respiratory depression, while the lower dose (20 μg) did not provide adequate analgesia. Clinical studies have investigated the impact of various parameters on the pharmacokinetic profile of fentanyl delivered by the system. The amount of fentanyl absorbed by patients was found to be directly proportional to the magnitude of current applied by the system, with a 170 μA current producing absorption of approximately 40 μg fentanyl and a coefficient of variation similar to that of i.v. fentanyl infusion (22% and 23%, respectively).

A separate study found that fentanyl absorption was also dependent upon the duration of treatment; approximately 40% of the 40 μg dose of fentanyl was absorbed in the first hour of treatment, and nearly 100% of the 40 μg dose was absorbed by 10 h of treatment (Fig. 3). Although the reasons for the increase in fentanyl absorption over time are not entirely clear, it may result from reversible alterations in the electrical conduction properties of skin that occur during exposure to electric current from the system. Absorption of fentanyl was not affected, however, by variations in the frequency of dosing or patient characteristics, such as age, gender, ethnicity and weight.

Clinical efficacy and safety

The fentanyl ITS has been evaluated in the treatment of acute, moderate-to-severe postoperative pain in adult patients undergoing orthopaedic, abdominal or thoracic surgery in four controlled phase III clinical trials. Initial assessments in three randomized, placebo-controlled clinical trials found the fentanyl ITS to provide pain relief superior to placebo (Table 3). Patients were treated for up to 24 h with the fentanyl ITS (40 μg fentanyl in 10 min; maximum, 240 μg h⁻¹) or a placebo system containing modified electronic circuitry to prevent iontophoretic dosing. A smaller proportion of patients in the fentanyl ITS group withdrew from the studies because of inadequate pain control compared with the placebo group (Table 3). The percentages of patients who withdrew because of inadequate analgesia in Studies 2 and 3 (25% and 29%, respectively) may have been higher than expected, as patients were unfamiliar with this novel analgesic modality. As a result, patients may have withdrawn from the studies because of inadequate analgesia to receive analgesia through an accepted method of pain control.

Patients who were treated with the fentanyl ITS also reported lower pain intensity scores on a VAS at the last assessment compared with patients treated with placebo (Table 3). These scores represented the mean pain intensity at the last recorded time point, and it is not surprising that the between-group differences were significant but not particularly large, as postoperative acute pain intensity characteristically decreases over time regardless of treatment. Furthermore, these data included mean pain intensity at last assessment scores from patients who dropped out of the study.

### Table 3

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fentanyl ITS (n=76)</td>
<td>Placebo (n=25)</td>
<td>Fentanyl ITS (n=142)</td>
</tr>
<tr>
<td>Rate of discontinuation attributable to inadequate analgesia (%)</td>
<td>7</td>
<td>38</td>
<td>0.003</td>
</tr>
<tr>
<td>Rate of discontinuation attributable to an adverse event (%)</td>
<td>3</td>
<td>0</td>
<td>NC</td>
</tr>
<tr>
<td>Mean pain intensity at last assessment</td>
<td>28*</td>
<td>37*</td>
<td>0.016</td>
</tr>
</tbody>
</table>
study because of inadequate analgesia, which may have diminished between-group differences in pain intensity scores. Similar proportions of patients in the fentanyl ITS and placebo groups withdrew from the studies because of an adverse event (Table 3).13 16 57

Results of an active-comparator phase III trial (N=636) found the fentanyl ITS to provide postoperative pain control equivalent to a standard regimen of morphine i.v. PCA.56 Patients were randomized 1:1 to receive either the fentanyl ITS (40 μg fentanyl in 10 min; maximum, 240 μg h \(^{-1}\)) or morphine i.v. PCA (1 mg morphine in 5 min; maximum, 10 mg h \(^{-1}\)) for a maximum treatment period of 72 h. A similar percentage of patients in each group (73.7% of patients in the fentanyl ITS group and 76.9% in the morphine i.v. PCA group; difference=–3.2; 95% CI, –9.9%, 3.5%) rated their method of pain control in the first 24 h of treatment as ‘excellent’ or ‘good’ (defined as treatment success), and >80% of patients in each group rated their method of pain control as ‘excellent’ or ‘good’ in the second and third 24 h periods of continued treatment. The difference between treatment groups in patients who withdrew from the study for any reason (fentanyl ITS group, 25.9%; morphine i.v. PCA group, 25.0%; P=0.78) or because of inadequate analgesia (fentanyl ITS group, 15.2%; morphine i.v. PCA group, 10.3%; P=0.07) was not significantly different. The pain intensity scores (VAS) at the last patient assessment in the first 24 h of treatment were also not different in the fentanyl ITS and morphine i.v. PCA groups (32.7 vs 31.1, respectively; estimate for difference=1.6; 95% CI, –2.61, 5.81).56

The safety record of fentanyl ITS shows it has been associated with adverse events that commonly occur as a result of systemic opioid administration, but results of four controlled phase III clinical trials indicated that these adverse events were primarily of mild-to-moderate severity.13 16 56 57 In the active-comparator phase III clinical trial, the most commonly occurring adverse events, including nausea, vomiting, pruritus and headache, were reported at a similar frequency between patients in the fentanyl ITS and morphine i.v. PCA groups.56 Respiratory depression is one of the most serious complications that may result from systemic opioid therapy. Importantly, there have been no reported incidents of clinically relevant respiratory depression, defined as <8 breaths min \(^{-1}\) for 1 min and excessive sedation, among the 1142 patients who have been treated with the fentanyl ITS in controlled and uncontrolled clinical studies.15 Similarly, only one patient in the active-comparator trial who received treatment with morphine i.v. PCA was withdrawn from the study for this reason.56

Skin reactions may occur at the application site of the fentanyl ITS as a result of iontophoretic drug delivery. Among patients treated with the fentanyl ITS in the four controlled phase III clinical studies, the most common application-site reactions were erythema, vesicles and itching, which were reported as adverse events in <15% of treated patients.13 16 56 57 Most application-site reactions were of mild-to-moderate severity and resolved quickly without requiring treatment. It is not clear, however, how many cases may have been of a more prolonged nature.

**Considerations for clinical application of the fentanyl ITS**

Several features of the fentanyl ITS may contribute to its usefulness in the management of acute postoperative pain. The pre-programmed nature of the fentanyl ITS prevents adjustment of the quantity of fentanyl delivered, which may be perceived as both a positive and negative feature. Pre-programming eliminates the potential for manual programming-related errors or tampering resulting in improper delivery of medication, thereby enhancing patient safety. However, it also eliminates the possibility for dosing adjustments, which may be potentially limiting for patients with unique or excessive opioid needs. Patient safety is ensured by the ‘lock-out’ period during analgesic delivery to prevent overmedication from excessive dosing, which is, of course, a feature of all PCA systems. In addition, the non-invasive nature of iontophoretic drug delivery avoids the risk of needle-related injury and infection to both healthcare professionals and patients alike. Furthermore, the compact size and disposable nature of the fentanyl ITS may be convenient for use in pain management programmes. The self-contained system does not require patient attachment to a PCA pump or tubing, thus the fentanyl ITS should not interfere with patient mobility or rehabilitation during postoperative convalescence.

Alongside considerations of clinical evidence, the cost-effectiveness of medical interventions plays a sizeable role in healthcare decision-making. Cost evaluations of pain management must examine many direct and indirect expenses incurred by treatment. For example, the costs associated with i.v. PCA include those directly associated with the PCA pump (e.g. costs related to purchase or rental, maintenance and replacement) and consumable materials (e.g. medication, i.v. tubing) in addition to labour costs (e.g. training to use the device, set-up of the apparatus, loading of analgesic, programming the pump). The cost of treatment using the fentanyl ITS remains undetermined, yet one may speculate that the purchase price of the system would constitute the majority of expenses associated with its use. Labour costs, other than standard clinical monitoring after operation would be expected to be minimal, as there is no requirement for programming or assembly of the system. Because the system is discarded after a single use, no resources would be required for maintenance or repair. The exact cost of the fentanyl ITS is awaited with interest.

There are some limitations associated with the use of the fentanyl ITS in postoperative pain management. One potential limitation is the inability to adjust the dosing parameters with the fentanyl ITS, which may impact pain management in patients with considerable opioid needs.
In addition, the system is associated with limitations that are common to PCA in general. A patient must be able to understand instructions for operation of the system and sufficiently alert following surgery to be suitable candidates for self-management of postoperative pain. The patient will, of course, require the same regular clinical monitoring after operation that is required for other opioid-PCA systems. In addition, a patient must have the necessary upper body mobility to activate the system once it is attached.

Conclusions
Pain management is an essential element of patient care and rehabilitation following surgery, as results of clinical studies have shown that effective pain control can reduce patient morbidity and its associated healthcare costs, in addition to minimizing patient anxiety and physical discomfort. However, PCA strategies that are commonly used to treat postoperative pain introduce some risk of potentially dangerous complications resulting from the use of an invasive method of drug administration and the requirement for manual programming of a PCA pump. In addition, existing PCA devices may limit patient mobility and consume substantial resources dedicated to use and maintenance of the systems.

The fentanyl ITS is an advanced pain management system that may address many of the concerns of safety and convenience with existing PCA modalities through the use of a pre-programmed and disposable drug delivery system. The use of iontophoretic technology allows for non-invasive drug delivery by the transdermal route, with a pharmacokinetic profile that is appropriate for acute pain management.

The fentanyl ITS was shown to be an equivalent method of pain control to a standard regimen of morphine i.v. PCA in an active-comparator phase III trial. Several controlled phase III clinical studies found the system to provide effective relief of acute pain in adult patients following major surgery, with an expected incidence of side effects that are commonly associated with opioid therapy. No incidents of clinically relevant respiratory depression have occurred in patients treated with the fentanyl ITS in any of the clinical studies that evaluated its use. One published study to date has evaluated the use of the fentanyl ITS for postoperative pain management in comparison to morphine i.v. PCA. Future studies should assess the fentanyl ITS in patients across populations divided according to age, body weight and type of surgery to evaluate the potential impact of pre-programmed dosing on efficacy and safety. In addition, the duration and severity of application-site reactions, in particular erythema, should be studied further. The fentanyl ITS has the potential to become a valuable alternative in the management of acute postoperative pain.

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