

# Special REPORT

## Transdermal PCA in Acute Postoperative Pain Management: *A Critical Evaluation of the Investigational IONSYS System*

Acute postoperative pain continues to be undertreated, with up to 75% of patients in the United States failing to receive adequate postoperative pain relief.<sup>1,2</sup> Postoperative pain management was revolutionized with the introduction of patient-controlled analgesia (PCA) using IV or epidural delivery routes more than 20 years ago.<sup>3</sup> Opioids are the primary treatment for acute pain management,<sup>4</sup> either alone or increasingly as part of a multimodal analgesic strategy—characterized by administration of 2 or more drugs (eg, opioid and nonopioid analgesics, used in combination) that act by different mechanisms, and along different pain pathways—an approach that is recommended by the American Society of Anesthesiologists (ASA) and the American Pain Society.<sup>5,6</sup> However, existing PCA modalities have limitations that include invasive access, challenges in titration of analgesic effect, cumbersome pump technologies, impaired patient mobility, and limited drug preparations that have been associated with programming, medication, and dosing errors.

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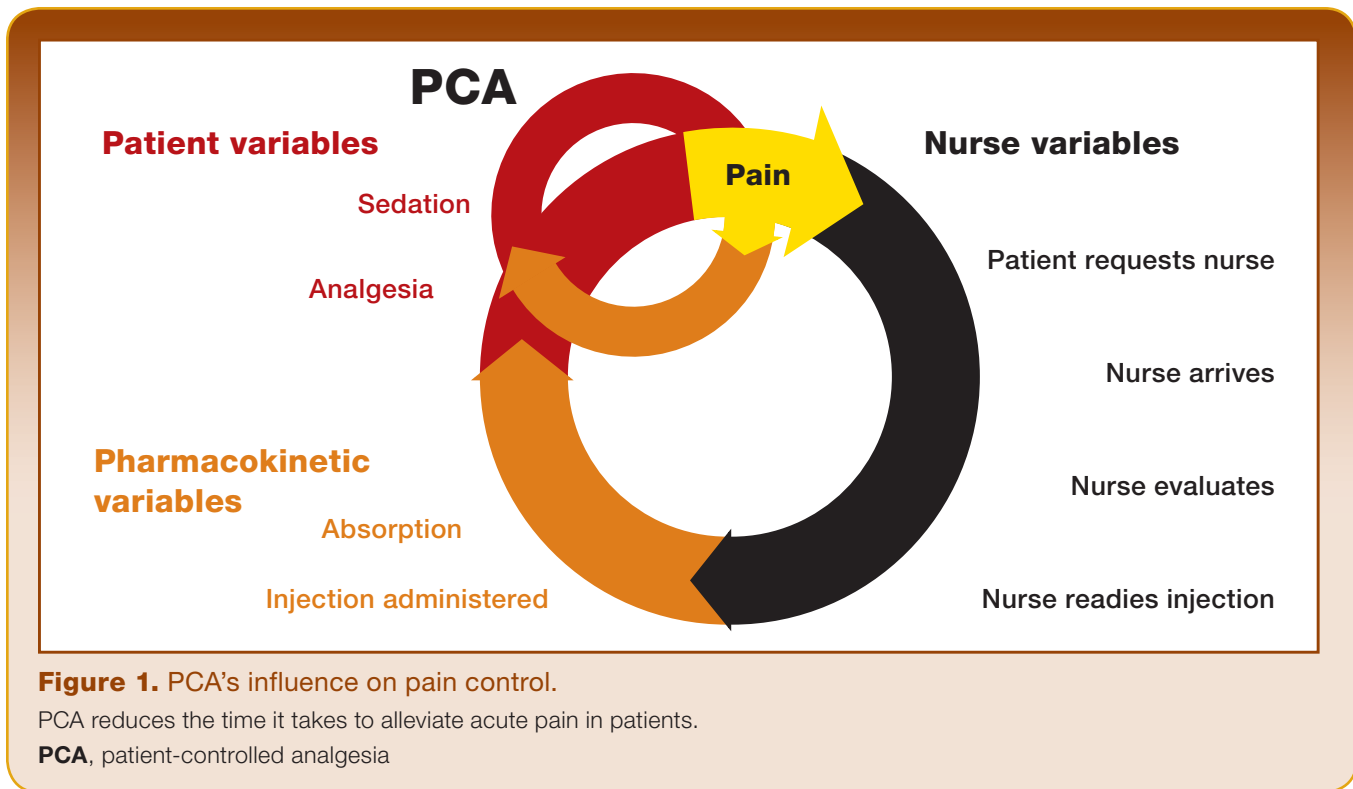
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Despite advances in pain management technology, the advent of acute pain services, and professional practice guidelines aimed at improving postoperative pain management, inadequacies and treatment gaps still exist, and improvement remains a priority.<sup>7</sup>

An analgesic intervention that might help to mitigate clinician concern is the fentanyl iontophoretic transdermal system (IONSYS), a credit card-sized, self-contained, and preprogrammed investigational product candidate intended to provide pain relief for adult inpatients requiring opioids following surgery.<sup>8</sup> It is a needle-free system that is applied to the skin on the upper arm or chest.<sup>8</sup> A generally imperceptible electrical current then delivers a small dose of fen-

tanyl directly through the skin and into the systemic circulation. The FDA approved IONSYS in 2006; however, it was never launched in the United States due to required changes in manufacturing. The enhanced design will be reviewed by the FDA in the near future for use in patients with moderate to severe postoperative pain.

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## Burden of Acute Postoperative Pain

More than 48 million inpatient surgeries and roughly 35 million outpatient surgeries are performed annually in the United States, and the magnitude of unrelieved acute postoperative pain is substantial.<sup>4,9,10</sup> Unrelieved pain can have profound implications and inadequately managed acute postoperative pain can result in negative clinical (eg, myocardial infarction, infection, pneumonia, poor wound healing, demoralization) and medical outcomes (eg, extended hospital length of stay, readmissions, patient dissatisfaction, perception of negative hospital performance, and increased health care utilization costs).<sup>4</sup> Given the problem of insufficient pain relief, treatment regimens now include the use of multimodal analgesia to control postoperative pain and potentially improve postoperative recovery.<sup>11</sup>

## Elements of Multimodal Analgesia

A multimodal approach that incorporates opioid-based PCA is a principal element of acute pain management during the postoperative period.<sup>12</sup> The 2012 ASA Practice Guidelines for Acute Pain Management in the Perioperative Setting recommend the consideration of acetaminophen, oral cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs), nonselective NSAIDs, and calcium channel  $\alpha_2\delta$  antagonists (ie, gabapentin and pregabalin) as part of an acute postoperative multimodal pain management regimen.<sup>5</sup> Patients should receive around-the-clock (ATC) doses of coxibs,

NSAIDs, or acetaminophen unless contraindicated.<sup>5</sup> Regional anesthetic techniques, including peripheral nerve blockade, should be considered; dosing regimens, route of administration, and therapy duration should be individualized to balance considerations of effectiveness and risk for adverse events (AEs).<sup>5</sup> Drugs with a primary indication other than analgesia (eg, anti-convulsant medications) are sometimes used as part of a multimodal strategy.

While opioids remain an important part of the foundation of pharmacological management of moderate to severe pain during the postoperative period,<sup>13</sup> opioid-reducing regimens of ATC nonopioids are considered most appropriate.<sup>5</sup> Opioids endure as an important analgesic component for the systemic treatment of postoperative pain,<sup>12</sup> but the best delivery route of therapeutic agents depends on many factors including the physician's level of expertise as well as patient characteristics. Evidence shows that when compared with conventional opioid analgesia (eg, IV, subcutaneous, intramuscular), PCA with opioids provides a greater analgesic effect, even when the amount of opioids consumed is similar between the 2 methods; and it also is the preferred treatment modality among patients.<sup>14</sup> PCA also can be used in conjunction with an opioid-sparing multimodal treatment regimen.

## PCA Modalities and Practices

The basic tenet of PCA dictates that patients should have direct control of their pain management<sup>14</sup> and may benefit from

doing so.<sup>15</sup> Severe acute pain is best treated with intermittent, small doses of opioids that are delivered immediately when needed (Figure 1). This allows for rapid titration of analgesic effect and provides more effective pain relief than conventional (eg, intermittent bolus intramuscular, IV, subcutaneous) opioid regimens.<sup>14,15</sup> The superior analgesic efficacy of IV PCA compared with intermittent intramuscular analgesia was demonstrated in a pooled-data analysis in which the incidence of moderate-severe pain with intramuscular analgesia was 67% (95% confidence interval [CI], 58.1%-76.2%) and severe pain was 29% (95% CI, 18.8%-39.4%). For PCA, the incidence of moderate-severe pain was 36% (95% CI, 31.4%-40.2%) and severe pain was 10% (95% CI, 8%-12.8%), respectively.<sup>16</sup> Data also have shown that fewer pulmonary complications are reported with IV PCA compared with other methods of opioid delivery (eg, IV, subcutaneous, intramuscular), and the risk for oversedation is reduced.<sup>14,17</sup>

After pain control has been established with a loading dose of IV opioids, PCA is used to sustain comfort by self-administering small amounts of analgesic medication within preset parameters.<sup>18</sup> Staff-programmed PCA pump settings regulate medication dosing and dosing frequency, the lock-out period between doses, and the maximum allowable dose per hour. Existing PCA modalities including IV PCA, patient-controlled epidural analgesia (PCEA), and patient-controlled regional anesthesia (PCRA) have varying benefits. For example, IV PCA has an acceptable efficacy and safety profile along with reports of high patient satisfaction.<sup>3</sup> Analgesia delivered through the epidural route (eg, PCEA, continuous infusion, bolus injection) supplies rapid analgesia and decreases systemic opioid exposure.<sup>3</sup> PCEA also allows patients to self-administer analgesia based on individual requisites.<sup>3</sup> Similarly, PCRA provides analgesia without systemic exposure to opioids and it can conveniently be used in an outpatient setting.<sup>3</sup> Similar to IV PCA and PCEA, PCRA also has the advantage of a no first-pass gastrointestinal effect but also a no first-pass hepatic effect.<sup>3</sup> The ASA recommends the use of therapeutic options like systemic opioid PCA, central regional (ie, neuraxial) opioids, and peripheral regional techniques after carefully considering patient profiles and clinicians' experience level, and the use of these modalities is preferred over prescribed as needed intramuscular opioids.<sup>5</sup> PCA is a standard of postoperative pain management and current modalities allow for use of complex regimens.

### Cost-Effectiveness Related to PCA

Medical expenses, unintended morbidity and mortality costs, and overhead expenses all affect the total cost of managing pain during the postoperative period. Actual costs associated with postoperative pain management include fixed costs, which remain stable despite volume of activity (eg, IV PCA pumps), and variable costs, which fluctuate according to volume (eg, analgesics, disposable supplies). Because the inadequate treatment of postoperative pain may result in chronic pain, it may be difficult to estimate the actual cost of postoperative pain management. Unfortunately, hospitals and health care providers usually are unaware of the actual costs

associated with providing services, and actual costs do not always equate to compensation for the institution or clinician.

The examination of cost-effectiveness evaluates the total benefits respective to the expenses and resources necessary for advances in pain management. For example, 1 study analyzed cost-effectiveness between PCA and intermittent intramuscular injections. In this study, PCA was the preferred modality compared with intermittent intramuscular injections because it was associated with a lower mean pain level over 24 hours and greater patient satisfaction.<sup>19</sup> While the mean drug and equipment cost for PCA was higher per patient compared with intermittent intramuscular injections, PCA retained clinical advantages over the traditional injection such as greater pain relief and patient satisfaction.<sup>19</sup>

With regard to IV PCA, direct costs include staff time, analgesics, infusion pumps, and tubing. Likewise, intangible costs that are associated with IV PCA include restricted mobility and patient discomfort. Indirect mortality and morbidity expenses for all modalities include expenses associated with insufficient pain management, medication errors, and staff-related injuries such as needlesticks. Examples of opportunity expenses include lost nursing time for pump programming, delays in setting up equipment, and consequent delays in patient discharge from the hospital.

When developing a regimen for postoperative pain management, an analysis of cost-effectiveness that scrutinizes resource utilization and labor costs related to these modalities, along with probable intangible, indirect, and opportunity costs is justified. The potential for pain relief is an important factor to consider when weighing the cost-benefits of a specific treatment modality.

### Clinical and Pharmacodynamic Characteristics of Opioids in PCA

Currently, opioids are the principal treatment for acute pain.<sup>4</sup> Morphine is the most commonly employed opioid in postoperative IV PCA (usual starting dose in opioid-naïve patients, 1 mg), followed in usage by hydromorphone (0.2 mg) and fentanyl (10 mcg); all are pure opioid agonists.<sup>18</sup> Best practice dictates that approximately equianalgesic dosing of opioids is employed to minimize the impact of medication errors. Although morphine is considered the gold standard for IV PCA,<sup>18</sup> its active metabolites—morphine-3-glucuronide and morphine-6-glucuronide—may accumulate insidiously in patients with renal impairment and have toxic effects owing to reduced excretion of the metabolite.<sup>20</sup>

Hydromorphone may be used as an alternative in morphine-intolerant patients or in those with altered renal function. Compared with morphine, hydromorphone is at least 5 times more potent; initial doses should be significantly lower for hydromorphone and ordered in milligrams.<sup>15</sup> Meperidine should be avoided for routine PCA because of an association with seizures, confusion and central nervous system stimulation, caused by its metabolism to an active form, normeperidine.<sup>15</sup>

Fentanyl has no active metabolites<sup>20</sup> and is highly lipophilic, which facilitates crossing the blood-brain barrier.<sup>21</sup> Small

**Table.** Patient-Controlled Modalities Used for the Management of Acute Postoperative Pain

Modality	Conveniences	Limitations
<b>Iontophoresis</b>	Noninvasive; rapid analgesia; convenient, small in size, no required cables or pump; no programming by hospital staff required; no first-pass GI effect; limited time and resources required for administration; patient controlled	Not appropriate for patients with skin disorders or injuries that prevent application; individualization of dosing limited to frequency of dosing
<b>IV PCA</b>	Rapid analgesia; patient controlled; programmable	Invasive; pump apparatus, tubing, and power cables may limit patient mobility; extensive staff time and resources required for administration; requires programming by staff; potential for IV line occlusions, programming and drug errors
<b>PCEA</b>	Rapid analgesia; patient controlled; programmable	Invasive; pump apparatus, tubing, and power cables may limit patient mobility; extensive staff time and resources required for administration; requires programming by staff
<b>PCRA</b>	No first-pass hepatic effect; minimized systemic opioid requirements	Technique generally limited to orthopedic surgery patients; further development of PCRA pumps needed; efficacy and safety needs further evaluation

GI, gastrointestinal; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PCRA, patient-controlled regional analgesia  
From reference 3.

positively charged molecules are ideal iontophoretic agents. Hence, fentanyl hydrochloride (HCl) is well suited for iontophoretic delivery.<sup>22</sup>

Furthermore, fentanyl exhibits a satisfactory AE profile. Hutchinson and colleagues reported that patients in the postoperative period who received IV PCA fentanyl had a low rate of common opioid-related AEs (eg, nausea, vomiting, pruritus, urinary retention, sedation).<sup>23</sup> The same study revealed that during postoperative days 1 and 2, the IV PCA fentanyl group also had an acceptably low median pain score.<sup>23</sup>

Because the kidneys excrete metabolites of most opioids, the absence of active metabolites with fentanyl may make it a reasonable choice for patients with renal impairment.<sup>24</sup> In critically ill patients, fentanyl has a prolonged clearance (half-life up to 25 hours) that should be taken into consideration. In addition to fentanyl, drugs with the relatively safest analgesic pharmacologic profiles for use in patients with impaired kidney function include alfentanil, ketamine, and buprenorphine.<sup>24</sup> Drugs also used in the presence of renal failure but with special precautions—usually dose reductions—include amitriptyline, gabapentin, bupivacaine, and clonidine.<sup>24</sup> NSAIDs and aspirin should not be used in the presence of chronic renal failure because of the risk for significant toxicity.<sup>24</sup> In any patient population, postoperative renal function may differ markedly from preoperative renal function and clinicians should be vigilant for renal function changes.

### Limitations of IV PCA

When accurately prescribed and effectively monitored, PCA is an effective and safe way to control acute pain.<sup>15</sup> However, PCA also is complex and prone to error.<sup>3</sup> PCA is associated with numerous system-related complications and programming errors.<sup>3</sup> In fact, device malfunction is a major cause of reported AEs with IV infusion pumps. Of 2,009 IV PCA-related events reported to the FDA's Manufacturer and User Facility Device Experience (MAUDE) voluntary medication error reporting program during a 2-year period, 1,590 (79.1%) were classified as possible device-safety events.<sup>25</sup> A retrospective analysis of MEDMARX, an Internet-accessible, voluntary medication error reporting program, found that PCA medication errors consequently are associated with higher relative risk for patient harm compared with non-PCA medication errors, and may occur during all phases of the medication use process.<sup>26</sup>

The increased focus on patient satisfaction in the hospital setting, led by the Centers for Medicare & Medicaid Services and the Agency for Healthcare Research and Quality, emphasizes the need for the optimal delivery of PCA. The Hospital Consumer Assessment of Healthcare Providers and Systems' (HCAHPS) national standard survey monitors patients' perspectives on hospital care.<sup>27</sup> Increasingly, this survey—which includes an assessment of patient satisfaction—is being used to dictate reimbursement at risk.<sup>27</sup> In fact, patient satisfaction with

pain management in the hospital is one of the 6 summary measurements used to determine the at-risk reimbursement under HCAHPS.<sup>28</sup>

Complications associated with PCA include a troublesome profile of common  $\mu$ -agonist opioid-induced AEs including respiratory depression, nausea, vomiting, pruritus, sedation, and confusion.<sup>18</sup> There also is the potential for complications related to the IV line itself (eg, occlusions) and catheter infiltration into subcutaneous tissue, or programming and medication errors—any of which can result in potentially serious AEs, including oversedation, respiratory depression, and under-treated pain (Table).<sup>3,15</sup>

Specific clinical disadvantages of IV PCA are that it is invasive, hinders patient mobility, requires external supplies (eg, tubing, power cables, drug cassettes) and the necessity of pump apparatus and programming, and extensive staff time and resources. In terms of patient comfort, analgesic gaps can occur while patients are waiting for medication during the transition from one analgesic modality to another. PCA delivery also requires a staff of expert clinicians including pharmacists, physicians, nurses, and physician assistants. The infrastructure must be present in order to safely and effectively deliver PCA—thus, a substantial commitment in resources is necessary. Furthermore, PCA by proxy errors, in which an unauthorized party activates the analgesic pump's dosing mechanism, delivering analgesic medication to the patient, are another potentially serious issue within PCA delivery. PCA by proxy errors can result in serious AEs including oversedation, respiratory depression, and death.<sup>17</sup>

### Limitations of PCEA and PCRA

Similar to IV PCA, PCEA requires a staff-programmed pump and a highly qualified anesthesia provider to insert a catheter into the desired epidural location.<sup>3</sup> In addition to the need for extensive hospital staff for administration, PCEA also requires manual programming, increasing the risk for serious programming and medication errors.<sup>3</sup> PCEA's pump, tubing, and power cables discourage patient mobility, and there also is a risk for occlusions.<sup>3</sup> Analgesic administration via the epidural route also is associated with catheter dislodgement and migration within the epidural space; in fact, 17% of epidural catheters fail due to unexpected dislodgement.<sup>29</sup> PCRA also possesses certain limitations. For example, in addition to being invasive, PCRA in an unmonitored setting is associated with an increased risk for complications such as leaking or dislodgement of indwelling catheters and infection.<sup>3</sup> PCRA is usually restricted for use in orthopedic surgery patients; this modality also requires an advanced hospital staff to set up perineural catheters.<sup>3</sup>

### Limitations of Other Routes of Opioid Administration

While oral administration of opioids for the treatment of moderate to severe pain is both convenient and noninvasive, it is usually contraindicated in the immediate postoperative period.<sup>12</sup> Oral opioids also possess a delayed onset of action; poor absorption in the gastrointestinal tract and a powerful first-pass effect cause a variable period of action compared with parenteral opioids.<sup>12</sup>

As such, greater doses of opioids (eg, morphine and meperidine) are required for oral administration than for the parenteral route.<sup>30</sup> Furthermore, because the optimal analgesic dose varies among patients, overdose or the undertreatment of pain are potential risks with this route of administration.

The intramuscular route is associated with painful administration<sup>10</sup> as well as ineffective pain control compared with other modalities (ie, PCA, epidural).<sup>16</sup> The intramuscular administration of analgesics is characterized by unpredictable absorption as there is a 30- to 60-minute lag to peak effect followed by a sudden drop in action. The intramuscular route has another troubling element—when the opioid finally peaks, patients often are alone and can experience oversedation, vomiting, and aspiration.<sup>4</sup>

### Iontophoretic Transdermal Delivery

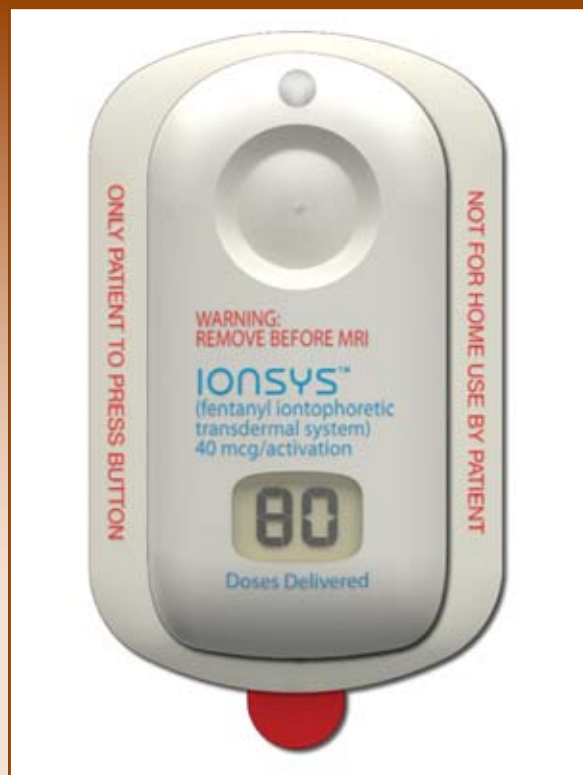
Transdermal drug delivery, like parenteral delivery, avoids first-pass hepatic metabolism and obstacles associated with oral analgesics following surgery (eg, vomiting, nausea, and difficulty swallowing).<sup>31</sup> For the delivery of analgesics, transdermal modalities operate as a drug reservoir that determines the amount of drug transfer.<sup>32</sup> Transdermal iontophoresis is a method that employs a subtle electrical current to deliver ionized drug molecules across the skin and into the circulation.<sup>31</sup>

With iontophoresis, neutral or cationic agents are positioned below an anode and anionic agents are fixed below a cathode, and a low current density and low voltage is applied, causing ions to be repelled through and into the skin.<sup>32</sup> The skin acts to complete the circuit as electric currents move from the anode to the cathode.<sup>31</sup> Specifically, the anode causes cationic therapeutic agents to be moved into and through the skin, and extracts anions from the tissue beneath the skin back into the anode.<sup>32</sup> Within the cathode, anionic buffer ions are sent through the skin and the tissues' cations migrate into the cathode.<sup>32</sup> As such, an active transdermal system that uses iontophoretic drug delivery offers patients control over analgesic dosing along with convenient administration and rapid analgesic delivery without some of the shortcomings associated with IV and epidural routes.<sup>31</sup>

### Iontophoretic PCA

IONSYS is a noninvasive device that employs iontophoretic technology and is designed for PCA via the transdermal route (Figure 2).<sup>33</sup> IONSYS is adhered to the patient's skin with an adhesive backing. To deliver a dose of fentanyl, the patient can press the dosing button twice within 3 seconds; an audible tone will signal the start of delivery of each dose; and a rapidly blinking green light will remain on throughout the 10-minute dosing period.<sup>33</sup> IONSYS activation produces a small electrical voltage between the anode and cathode. This causes positively charged fentanyl molecules located in the anode hydrogel reservoir to be repelled from the positively charged anode surface and to be delivered through the skin into the systemic circulation.<sup>31</sup> In contrast to existing PCA modalities, iontophoretic transdermal delivery does not require infusion pumps or indwelling catheters to deliver medication, which encourages patient mobility in the critically important postsurgical period.<sup>3</sup>





**Figure 2.** Enhanced IONSYS device.

The credit card–sized, preprogrammed system delivers a small dose of fentanyl through the patient’s skin and into the systemic circulation.

From reference 33.

IONSYS delivers 40 mcg of fentanyl per on-demand dose over a 10-minute period, with up to 6 doses available per hour.<sup>8</sup> As such, IONSYS performs for as long as 24 hours or for a maximum of 80 doses, whichever takes place first; additional IONSYS systems can be used after 24 hours if needed for up to 3 days.<sup>3</sup> The enhanced IONSYS device features an improved display, which helps clearly show to health care practitioners how many doses have been delivered. IONSYS eliminates IV line complications, which can lead to analgesic gaps, by supplying instantaneous dosing on patient demand, providing consistent analgesia and eliminating potentially painful waiting periods between requests for analgesia and drug administration.

IONSYS also features preprogrammed dosing, which eliminates the potential for medication dosing errors. PCA medication errors have been the focus of hospital-directed safety alerts issued by the Institute for Safe Medication Practices and the Joint Commission, and remain a critical concern.<sup>34</sup> For example, using MEDMARX data, the most common cause of IV PCA errors was human-related (accounting for 322.91 errors per 10,000 patients); followed by equipment-related (102.23 overall errors per 10,000 patients).<sup>35</sup> Using MAUDE data, the

percentage of human-related errors reported to have inflicted patient harm was 48.1%.<sup>25</sup> MAUDE data also indicates that the percentage of device-related errors reported to have inflicted patient harm was 0.5%.<sup>25</sup> Furthermore, IONSYS’ compact design also eliminates the necessity for unwieldy equipment that requires nursing staff attention and may restrict patient mobility because the patient is tethered by IV tubing, an IV pole, and the IV PCA pump apparatus.

### Clinical Considerations With IONSYS

Pharmacokinetic (PK) evaluations of IONSYS in dosing frequency studies have demonstrated that it has a PK profile similar to that of IV PCA fentanyl, but with a slower rise, lower peak level, and less fluctuations.<sup>36,37</sup> Systemic absorption of the fentanyl delivered by IONSYS increases as a function of time; this increase appears to be independent of dosing frequency.<sup>8</sup> Subtherapeutic passive absorption with IONSYS is minimal compared with transdermal delivery; IONSYS leaves no significant skin depot of fentanyl with discontinuation of the system, and serum levels fall almost immediately (Figure 3).<sup>8,38</sup> After 24 hours or 80 doses have been administered, IONSYS deactivates and cannot supply additional doses to the patient.<sup>8</sup>

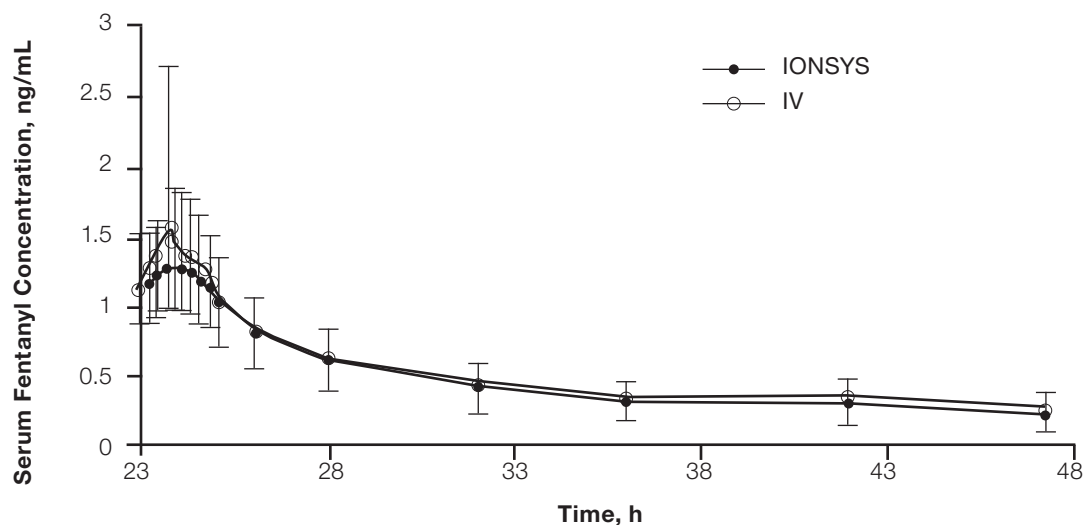
IONSYS is designed to be applied to the skin on the upper arm or chest. The quantity of fentanyl HCl delivered by activation of the system has been demonstrated to be independent of patient age, sex, body mass index, or race, but is dependent on the location of the device on the body, with the ideal application sites being the upper outer arm or chest of patients.<sup>39</sup>

### Ensuring Safe and Effective PCA

Because IONSYS is intended only for use among hospitalized patients in the acute setting, the potential for misuse may be limited compared with the potential for misuse of the fentanyl transdermal patch or other opioids.<sup>3</sup> To ensure proper usage, medical personnel are required to remove the IONSYS system prior to hospital release and dispose of it.<sup>8</sup> Nevertheless, appropriate opioid selection can mitigate risks,<sup>40</sup> and developing PCA patient-selection criteria (eg, evaluation of medically complicated patients, identification of patients with a need for a basal infusion, such as those who are opioid-tolerant) is one of the most overlooked but effective mechanisms to reduce risk for opioid-related AEs.<sup>15</sup> In addition to clarifying the patient groups that are most likely to benefit from a particular PCA modality, targets for intervention in safe opioid analgesia are prescribing errors, staff training on use and protocols, monitoring, and patient education.<sup>15</sup>

### Conclusion

Opioids remain the most commonly used analgesics in postoperative pain management, especially for the treatment of moderate to severe pain. A multimodal approach that includes opioid-based PCA is an important tenet in managing acute postoperative pain.<sup>12</sup> While the ideal mechanism of delivery depends on physicians’ expertise and the patient, data has shown that when compared with conventional opioid analgesia (eg, IV, subcutaneous, intramuscular), PCA with opioids is the preferred treatment modality among patients.<sup>14</sup> However,



**Figure 3.** IONSYS vs IV fentanyl during last hour and at termination.

Comparison of IONSYS and IV fentanyl during the last hour and at termination of the following treatment: 40 mcg of IONSYS was administered in 2 sequential doses over 20 minutes every hour for 23 hours and 20 minutes, and 80 mcg of IV fentanyl was administered over 20 minutes every hour for 23 hours and 20 minutes.

From reference 8.

certain PCA modalities have disadvantages, including invasiveness (eg, IV PCA, PCRA), risk for infection (eg, PCRA), and medication or programming errors (eg, IV PCA, PCEA).<sup>3</sup>

The compact, self-contained, preprogrammed IONSYS system may limit the possibility for a number of medication and system-related events, including manual programming

errors, which have been associated with potentially serious clinical consequences.<sup>25,26</sup> Unlike other PCA modalities, IONSYS is noninvasive, which promotes patient mobility during the postsurgical period. Within a multimodal pain management strategy, IONSYS may be a reasonable choice for analgesia in adult patients after a range of major surgical procedures.

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