Iontophoretic transdermal system using fentanyl compared with patient-controlled intravenous analgesia using morphine for postoperative pain management†

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Background. The fentanyl iontophoretic transdermal system (fentanyl ITS) enables needle-free, patient-controlled analgesia for postoperative pain management. This study compared the efficacy, safety, and ease of care of fentanyl ITS with patient-controlled, i.v. analgesia (PCIA) with morphine for postoperative pain management.

Methods. A prospective, randomized, multicentre trial enrolled patients in Europe after abdominal or orthopaedic surgery. Patients received fentanyl ITS (n=325; 40.0 μg fentanyl over 10 min) or morphine PCIA [n=335; bolus doses (standard at each hospital)] for ≤72 h. Supplemental i.v. morphine was available during the first 3 h. The primary efficacy measure was the patient global assessment (PGA) of the pain control method during the first 24 h.

Results. PGA ratings of ‘good’ or ‘excellent’ were reported by 86.2 and 87.5% of patients using fentanyl ITS or morphine PCIA, respectively (95% CI, −6.5 to 3.9%). Mean (sd) last pain intensity scores (numerical rating scale, 0–10) were 1.8 (1.77) and 1.9 (1.86) in the fentanyl ITS and morphine PCIA groups, respectively (95% CI, −0.38 to 0.18). More patients reported a system-related problem for fentanyl ITS than morphine PCIA (51.1 vs 17.9%, respectively). However, fewer of these problems interrupted pain control (4.4 vs 41.3%, respectively). Patients, nurses, and physiotherapists reported more favourable overall ease-of-care ratings for fentanyl ITS than morphine PCIA. Study termination rates and opioid-related side-effects were similar between groups.

Conclusion. Fentanyl ITS and morphine PCIA were comparably effective and safe.


Keywords: analgesia, patient-controlled; analgesia, postoperative; analgesics opioid, fentanyl; analgesics opioid, morphine; analgesic techniques, transdermal iontophoresis

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Patient-controlled intravenous analgesia (PCIA) is often considered the standard method of care for the treatment of acute postoperative pain.1–7 However, the preparation of pumps, syringes, and lines requires considerable staff time and resources.8 Patient mobility may also be restricted by the patient-controlled analgesia (PCA) pump and i.v. line, and programming errors, pump failures, and syringe errors may result in severe adverse events.9 To overcome these problems, a new, needle-free fentanyl
HCl iontophoretic transdermal system (fentanyl ITS, IONSYS™, Janssen-Cilag NV, Beerse, Belgium) has been developed that is pre-programmed to deliver a fixed dose of fentanyl (40.0 μg) across the skin, utilizing the process of iontophoresis.10 It is compact, self-contained, and self-adhesive, and it is applied to the patient’s upper outer arm or chest. While previous trials have demonstrated the fentanyl ITS to be superior to placebo11 12 and therapeutically comparable with a standard morphine PCIA dosing regimen for postoperative pain management,13–15 other elements important to the process of patient care, such as the convenience of use and the associated levels of patient and provider satisfaction, have not been thoroughly assessed. The system was recently reviewed in this journal.16 In this study, validated questionnaires were also included to assess the ease-of-care (EOC)/use and the level of satisfaction associated with each modality from the perspectives of patients, nurses, and physiotherapists.17 This multicentre European study further evaluates the efficacy and safety of the two modalities in patients undergoing major abdominal or orthopaedic surgery to simulate its use in a standard clinical practice setting. The primary aim of this study was to determine whether fentanyl ITS was non-inferior to morphine PCIA for the management of postoperative pain using a patient global assessment (PGA) of the method of pain control 24 h after the initiation of treatment.

Methods
This international, multicentre, open-label, randomized, comparative, parallel-treatment, phase IIIb study was conducted from June 14, 2004, to June 15, 2005, at 51 sites in 11 European countries (Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Spain, Sweden, Switzerland, and the UK). The study protocol was approved by ethical committees in each country, and patients provided written consent during the screening process. Prospective patients were screened within 2 weeks before surgery, and medical history, physical examination, and informed consent were obtained. Patients were instructed in the use of the fentanyl ITS and morphine PCIA pump, and were provided with education regarding pain management and pain assessment. To determine the patient’s pain management goal, they were asked to indicate the postoperative pain score (0=’no pain’ to 10=’worst possible pain’) that they felt would not interfere with required activities, so that recovery could occur more quickly. Eligible patients were ≥18 yr of age; ASA status I, II, or III; and scheduled to undergo general or regional anaesthesia (i.e. spinal anaesthetic with ≤4 h duration of action) for elective major orthopaedic or abdominal surgery requiring parenteral opioids for moderate or severe pain for at least 24 h after surgery.

Patients were screened in the recovery room after the operation, and included in the study if they were awake, alert, and breathing spontaneously for at least 30 min, with a ventilatory frequency of 10–24 breaths min−1 and a pulse oximetry reading (SPO2) of at least 90% (with or without supplemental oxygen), and able to answer questions and follow commands. Patients had to be comfortable [pain intensity ≤4 out of 10 on a verbal numerical rating scale (NRS)].

Patients were excluded from the study if they were known or expected to be opioid-dependent, had a chronic pain disorder, had an active skin disease, were pregnant or breast-feeding, were expected to require intensive care after the operation, or would be likely to require additional surgical procedures within 72 h.

Patients who satisfied the above requirements were randomized (1:1) to receive either the fentanyl ITS or morphine PCIA, utilizing an interactive voice response system implemented before the study. Randomization was stratified by country and by surgery type (orthopaedic surgery of the lower extremities, lower abdominal surgery, upper abdominal surgery, or pelvic surgery). Patients were considered enrolled after the first application of the fentanyl ITS or after the attachment and enabling of the morphine PCIA pump, which occurred in the recovery room immediately after baseline assessments at Hour 0.

In the recovery room, if required, they were titrated to an acceptable level of comfort with i.v. bolus doses of morphine. After at least 30 min, the study entry criteria were assessed, and qualifying patients were randomized to receive either fentanyl ITS or morphine PCIA. Pain management with fentanyl ITS or morphine PCIA continued for up to 72 h. The treatment and assessment schedule is described in Figure 1.

Fentanyl ITS was applied to the patient’s upper outer arm or chest, and was activated when the patient pressed the recessed, on-demand dosing button twice within 3 s. An audible beep and the flash of a red light-emitting diode (LED) indicated the initiation of dosing. The system is pre-programmed and used an imperceptible electrical field to deliver 40 μg fentanyl over 10 min, allowing up to six doses per hour for 24 h or a maximum of 80 doses, whichever occurred first. At the end of each 24 h period or after 80 doses, the fentanyl ITS was removed from the patient and a new system was applied to a different application site. During delivery of each fentanyl dose, the system did not respond to additional requests for dosing delivery.

PCA pumps were programmed for a specific dose and lock-out period according to the standard practice of each participating hospital. Across hospitals, the patient initiated the delivery of a bolus dose of morphine (up to 20 mg per 2 h and a maximum of 240 mg per 24 h) by pressing the PCA dosing button.

Supplemental analgesia (i.e. morphine bolus administration after the routine practice of each hospital) was available to patients in both the fentanyl ITS and the
morphine PCIA groups during the first 3 h after the initiation of treatment on the first day of the study. Patients requiring supplemental opioid analgesia beyond the first 3 h were discontinued from the study. Non-opioid analgesics, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs; including ketorolac), and COX-2 inhibitors were allowed intraoperatively and during the postoperative screening or treatment period, according to clinical judgement and institutional practice per normal procedures for each hospital.

The primary efficacy endpoint was the PGA of the method of pain control at 24 h. The following question was read aloud to the patient by a member of the investigator’s staff: ‘Overall, would you rate this patient-controlled analgesia method of pain control during the last 24 hours as being poor, fair, good, or excellent?’ PGA success was defined as a response of ‘good’ or ‘excellent’. PGAs were also performed at the 48 and 72 h time points for patients who remained in the study, according to clinical judgement and institutional practice per normal procedures for each hospital.

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Additional efficacy outcomes included the mean number of doses of study medication used by each patient and the percentage of patients who required supplemental analgesia. The number of doses delivered by each modality was recorded at the same time points as the intensity scores. The number of fentanyl doses delivered by patients in the fentanyl ITS group was estimated (1 LED flash = 1–5 doses).

EOC questionnaires were completed at 72 h or at the time of study medication discontinuation for patients, upon study completion for nurses, and after any session during the study for physiotherapists. The items on the patient, nurse, and physiotherapist questionnaires that contributed to Overall EOC scores had response choices on a six-point Likert scale ranging from ‘not at all’ (0) to ‘a very great deal’ (5). The Patient EOC Questionnaire has previously demonstrated acceptable validity and reliability, and included 23 items that are divided into seven subscales: Comfort With Device, Dosing Confidence, Knowledge and Understanding, Movement, Quality of Pain Control, Confidence With Device, and Satisfaction; higher scores indicated more favourable results. For the Patient EOC Questionnaire, Overall EOC...
was defined as the mean of the mean scores for all items on six of the subscales, excluding Satisfaction (the mean scores on the Satisfaction subscale were reported separately). The Nurse and Physiotherapist Questionnaire has previously demonstrated validity and reliability, and included 22 items that are divided into three subscales: Time-consuming, Othersome, and Satisfaction. The Overall EOC for the Nurse and Physiotherapist Questionnaires was defined as the mean of scores on the Time-consuming and Othersome subscales (the Satisfaction subscale was excluded from the Overall EOC and reported separately); lower scores indicated more favourable results. Satisfaction with each method of pain control was assessed for patients, nurses, and physiotherapists. Items on the Satisfaction subscale included response options on a six-point Likert scale ranging from ‘extremely dissatisfied’ (0) to ‘extremely satisfied’ (5); higher scores indicated more favourable results.

Vital signs and oxygen saturation level were recorded at the same time points as the intensity scores. Problems associated with the fentanyl ITS or with the i.v. line or PCA pump with morphine PCIA were reported by the patient and recorded by members of the hospital staff on a separate check-list during the course of the study. Adverse events, including the occurrence of clinically relevant respiratory depression, defined as the simultaneous occurrence of bradypnea (<8 bpm) and excessive sedation, were recorded as they occurred. Application-site reactions reported by the patient or noticed by the patient or members of the hospital staff at any time were recorded. In addition, members of the hospital staff performed a prospectively defined assessment for application-site reactions at 24, 48, and 72 h. With the exception of clinically relevant respiratory depression, adverse events were classified according to the COSTART Thesaurus.

It was estimated that a total sample size of 590 patients, randomized 1:1, would provide a probability of 80% to demonstrate the non-inferiority of fentanyl ITS to morphine PCIA based on the percentages of PGA ratings of success observed in a previous study, with a lower limit of 10% on the 95% CI for the difference (to detect clinically relevant differences) and a significance level of 0.025 one-sided. To allow for a 10% dropout rate, an enrolment of up to 650 patients was planned for this study. Patient data were evaluated using two-way analysis of variance for numerical data, with treatment and country as factors, or using the Cochran–Mantel–Haenszel general association test for categorical variables, controlling for country.

Efficacy and safety analyses were performed using data from patients for whom the study treatment was applied (intent-to-treat population). Analysis of the primary efficacy outcome, PGA of the method of pain control at 24 h, included the construction of a 95% CI of the between-treatment difference in PGA successes (ratings of ‘good’ or ‘excellent’). Non-inferiority was concluded when the lower bound of the 95% CI fell to the right of the pre-selected maximum allowable difference of −10%. The between-group difference in the percentages of patients who reported a PGA rating of ‘excellent’ was determined using ANOVA, with treatment and country as factors. Other efficacy measures were evaluated using tabulations and descriptive statistics, along with the 95% CI. Data are expressed as number of patients, mean (SD), standard error of the mean (SEM), or median with minimum and maximum. Probability values were considered significant at the 5% significance level for two-tailed tests.

**Results**

A total of 660 patients were enrolled [fentanyl ITS group (n=325); morphine PCIA group (n=335)] and progressed through the study (Fig. 2). An average of 13 patients participated in the study at each site (range, 1–41 patients). Patient characteristics were not significantly different between groups (Table 1). The majority of patients were Caucasian (95.6%), mean (SD) age of 53.3 (14.6) yr, and 94.2% of the patients were ASA physical status I or II. The distribution of type of surgery was similar between groups. A total of 26 patients in the fentanyl ITS group and 32 patients in the morphine PCIA group received a spinal anaesthetic with a duration of action of ≤4 h. Morphine PCIA settings varied between hospitals, but the dosage remained within the allowed maximum of 20.0 mg morphine every 2 h; the morphine dose ranged from 1.0 to 3.0 mg, and the lockout interval ranged from 5 to 20 min.

The percentages of patients who reported PGA ratings of ‘good’ or ‘excellent’ after the first 24 h were 86.2% for the fentanyl ITS group and 87.5% for the morphine PCIA group (95% CI, 84.0% to 88.5% vs 85.9% to 88.2%, respectively; 95% CI, 8.3 to 5.1%); 83.9% for the fentanyl ITS group and 87.5% for the morphine PCIA group (95% CI, 82.5% to 88.9% vs 88.3% to 90.3%, respectively; 95% CI, 4.8 to 3.2%); and at the last assessment (88.0% vs 89.3%, respectively; 95% CI, 6.1 to 3.6%). Physicians also reported similar investigator global assessment ratings of success between groups at 24 h (90.8% vs 89.9%, respectively; 95% CI, 9.3 to 5.4%), 48 h (83.0% vs 85.1%, respectively; 95% CI, 4.8 to 6.5%), 72 h (87.1% vs 89.3%, respectively; 95% CI, 4.7 to 11.0%), and at the last assessment (89.8% vs 89.3%; respectively; 95% CI, −4.1 to 5.3%).

Mean (SD) pain intensity scores on the NRS (scale, 0–10) at the last patient assessment after the first 24 h were similar in both groups [2.5 (1.78) for fentanyl ITS and 2.4 (1.91) for morphine PCIA; 95% CI, −0.18 to 0.38; Fig. 4]. Comparable mean (SD) pain intensity scores were...
also observed at the last patient assessment [1.8 (1.77) vs 1.9 (1.86); 95% CI, −0.38 to 0.18]. Mean pain intensity scores were also similar in both groups at each measured time point (Fig. 4). In addition, the percentage of patients whose actual pain intensity scores at 24 h were less than or equal to their pain management goal was comparable between fentanyl ITS and morphine PCIA groups (78.3 vs 78.7%; 95% CI for the difference in response, −6.8 to 5.9%).

The estimated mean (SD) total number of on-demand, 40 μg fentanyl doses per patient in the fentanyl ITS group was 46.2 (35.63) doses (range, 0–168). The estimated mean (SD) amount of fentanyl delivered per patient in the fentanyl ITS group was 1.9 (1.43) mg (range, 0.0–6.7 mg) over the study period (72 h). The mean (SD) amount of morphine delivered per patient in the morphine PCIA group was 54.7 (47.69) mg (range, 0–278 mg). The proportion of patients who required supplemental analgesia was similar between the fentanyl ITS and morphine PCIA groups (11.1 and 11.0%, respectively). The median number of doses of supplemental morphine analgesia used [1 dose (range, 1–10 doses) and 2 doses (range, 1–15 doses)] and the mean (SD) amount of supplemental morphine used per patient [7.5 (6.45) mg and 6.5 (6.28) mg, respectively; 95% CI, −1.93 to 3.93 mg] were similar between the fentanyl ITS and morphine PCIA groups. The percentages of patients who used concomitant analgesic medications were comparable between groups (Table 2).

The percentages of patients who dropped out of the study because of inadequate analgesia were comparable in the fentanyl ITS and morphine PCIA groups (3.4 and 2.4%, respectively; 95% CI, −1.6 to 3.6%), as were the percentages of patients who withdrew for any reason (11.4 and 11.0%, respectively; 95% CI, −4.5 to 5.2%; Fig. 2). No statistical differences in reasons for study discontinuation were observed.

Patients reported higher (more favourable) mean (SEM) Overall EOC scores for the fentanyl ITS compared with morphine PCIA [4.3 (0.03) vs 4.1 (0.03); P<0.001; Table 3]. Patients also reported higher (more favourable)
mean (SEM) scores for the fentanyl ITS compared with morphine PCIA on the Movement subscale [4.8 (0.03) vs 3.7 (0.07); P < 0.001; Table 3]. Nurses and physiotherapists reported lower (more favourable) mean (SEM) Overall EOC scores, and Bothersome and Time-consuming subscale scores, for the fentanyl ITS compared with morphine PCIA (Table 4). There was no significant difference in the patient level of satisfaction between groups [mean (SEM), 4.1 (0.06), 4.1 (0.05); P = 0.804]. However, nurses and physiotherapists reported higher (more favourable) mean (SEM) Satisfaction ratings for the fentanyl ITS compared with morphine PCIA [nurses, 3.8 (0.05), 3.5 (0.05); P < 0.001; physiotherapists, 3.7 (0.10), 3.5 (0.09); P = 0.021].

The incidence of commonly occurring (≥2%) adverse events was comparable between the two groups (Table 5). The percentage of patients for whom at least one adverse event led to study discontinuation was similar between groups (5.5 vs 6.9%, respectively). The most frequent adverse events leading to study discontinuation were nausea (1.5% of fentanyl ITS patients, 2.1% of morphine PCIA patients) and dizziness (0.3% of fentanyl ITS patients, 1.2% of morphine PCIA patients).

In both treatment groups, fewer than 5% of patients experienced serious adverse events (SAEs) related to study medication. In the fentanyl ITS group, one SAE (ileus) was judged to be possibly related to study medication, whereas in the morphine PCIA group, three SAEs (one event of somnolence and two episodes of hypoventilation) were judged to be very likely related to study medication, and one SAE (hernia) was judged to be possibly related to study medication. One patient in the morphine PCIA group died of brain metastasis and intracranial
hypertension during the study, which was judged to be unrelated to study medication.

Respiratory function was the primary safety measurement. No patient in the fentanyl ITS group experienced clinically relevant respiratory depression (bradypnea, <8 bpm, and excessive sedation); however, one case occurred in the morphine PCIA group. Mean and median vital sign values were similar for both treatment groups at all study time points; a minimum oxygen saturation level of 88% was recorded in 10 (3.1%) fentanyl ITS patients and 19 (5.7%) morphine PCIA patients.

Application-site reactions, the majority of which were erythaema, occurred in 44.3% of patients in the fentanyl ITS group, with some patients experiencing >1 application-site reaction. In 7 patients, there were 11 severe events (as determined by the investigator), but all other cases were mild to moderate in severity. All patients recovered from these severe application-site reactions during the study, except for one patient who had not yet recovered at trial termination. Therapy was initiated to treat four of the severe application-site reactions. Infusion-site reactions occurred in 6.6% of morphine PCIA patients, all of which were of mild-to-moderate severity.

At least one problem associated with the method of pain control was reported in 51.1% of patients in the fentanyl ITS group and 17.9% of patients in the morphine PCIA group. The most common (>2%) problems in the fentanyl ITS group were erythaema/discoloration, other (i.e. a problem other than those listed for clinicians to choose from), device malfunction or failure, itching, and oedema, whereas the most common problems in the morphine PCIA group were other (i.e. a problem other than those listed for clinicians to choose from), the alarm going off, device malfunction or failure, line pulled out, and pain at injection site. Pain control was interrupted as a result of 4.4% of the events reported in the fentanyl ITS group (range, 2.0 min to 4.5 h) and in 41.3% of the events reported in the morphine PCIA group (range, 5 min to 12 h).

**Discussion**

This study supports the findings of previous phase III and phase IIIb trials that demonstrated fentanyl ITS to be superior to placebo\(^{11,12}\) and non-inferior to a standard regimen of PCIA with morphine.\(^{13-15}\) In addition, this study demonstrated that the fentanyl ITS is appropriate for use in the context of multimodal therapy.

There was a <2% difference in success ratings of ‘good’ or ‘excellent’ between the treatments, which is well below the predetermined 10% lower bound of the 95% CI for the difference used to determine clinically relevant differences on the PGA of the method of pain control.
Results of this study compared favourably with those of a previous active-controlled trial. In that study, although patients were titrated to comfort with i.v. opioids before study enrolment, a specific level of pain intensity at study entry was not defined, as was the case in our study. This resulted in comparatively higher mean pain intensity scores at Hour 0 in that study, which may have contributed to the higher rates of patient withdrawal and lower rates of PGA ratings of success observed in both treatment groups. These findings highlight the importance of the appropriate titration of initial pain levels and the potential negative impact of inadequate titration on the success of pain management during the postoperative period.

All SAEs (regardless of incidence rate) that may have been related to study medication are reported.

An unexpected result of this study was the higher incidence of application-site reactions (44.3%) compared with that reported in the previous placebo-controlled and active-controlled trials (2.6–14.7%). The most likely explanation for this observed difference between the studies is that the current study utilized a separate form specifically for the reporting of application-site reactions, whereas previous studies included a check box for application-site reactions on the general adverse events form. Similar to previous studies, however, the severity of the application-site reactions was generally mild to moderate. Nonetheless, if pain management requiring opioids is needed for >24 h, a new fentanyl ITS should be applied to a different skin site to minimize the occurrence of local erythaema.

The higher incidence of erythaema was also primarily responsible for the between-group difference in the percentage of reported problems with the method of pain control. However, a smaller percentage of these system-related problems resulted in interruption of pain control in the fentanyl ITS group compared with morphine PCA, and these problems interrupted control for a shorter period of time. These data suggest that despite the higher incidence of reported problems, fentanyl ITS may have been a more reliable modality compared with morphine PCA.

As respiratory function was the primary safety assessment, it is worth noting that the incidence of clinically relevant respiratory depression was rare (no cases in the fentanyl ITS group and one in the morphine PCA group). In the previously published clinical trials (phase I, phase III, or phase IIIb), no cases of clinically relevant respiratory depression were reported in the 1142 patients who were treated with fentanyl ITS. Similar to the results from previous trials, nausea and vomiting were the most frequent side-effects in this study, with a similar incidence observed in both the fentanyl ITS and morphine PCA groups.

In contrast to the previous studies comparing fentanyl ITS and morphine PCA, this study aimed to be as close as possible to clinical practice. Therefore, not all hospitals used the same morphine PCA settings, because hospitals in different countries have different regulations and procedures for standard practice. Although this may be viewed as a limitation, use of these settings was supported by results of previous studies that have shown no significant differences in analgesia or side-effects using a maximum hourly dose (10 mg h⁻¹), as used in this study, and a range of lockout intervals from 5 to 20 min. In
addition, the variability in the PCIA settings used, along with the administration of concomitant non-opioid analgesics, may allow for wider generalization of our results to different standard analgesic practices.

A possible limitation of this study is the open-label design, as patients and investigators knew which method was being used. The open-label design was necessary to assess the EOC of the two methods of pain control. It is nevertheless difficult to know whether this may have favourably or negatively influenced patient judgement of the fentanyl ITS as the ‘new’ treatment to be assessed. Another possible limitation of this study is that morphine PCIA dosing regimens were not standardized across hospital sites, as discussed above. Although the specific spinal anaesthetics (duration of action ≤4 h) used during surgery for some patients (fentanyl ITS, 8.0%; morphine PCIA, 9.6%) were not recorded, it is unlikely that the inclusion of spinal anaesthesia significantly impacted the outcome of this study. It is also unlikely that between-group differences in the amount of morphine necessary to titrate patients to comfort upon study enrolment occurred, because patients were randomized in a double-blinded fashion to one of the two treatment groups after comfort had been achieved. That this trial was carried out at multiple sites in multiple countries can be seen as a positive characteristic, as it better represented an average European clinical setting.

Although previous studies have shown that patients prefer PCIA to conventional routes of administration (i.e. intramuscular), several safety concerns exist with PCIA, such as the risk of medication errors, syringe mix-ups, and errors in programming. Such errors have resulted in oversedation and patient death in some cases. Catheter infiltration and phlebitis may also occur with PCIA use, which may lead to i.v. line failure and improper dosing. Administration of PCIA also requires the patient to be attached to an i.v. line, a PCA pump, and oftentimes a pole, which may limit patient mobility. In addition, blocked cannulae can occur with PCIA, which may result in analgesic gaps. Administration of PCIA also requires staff time and resources for analgesic preparation, PCA set-up, and patient monitoring.

Fentanyl ITS offers many of the benefits of existing PCA modalities, in addition to other benefits not provided by i.v. PCA modalities. The non-invasive nature of fentanyl ITS minimizes potential needle-related complications, and pre-programming of the system eliminates the risk of potentially dangerous adverse effects because of programming errors. Transdermal application with the fentanyl ITS also eliminates the risk of analgesic gaps related to catheter infiltration and blocked cannulae. Fentanyl ITS is self-contained and is discretely attached to the patient’s upper, outer arm or chest. The system appears to be easy for patients to use and for nurses and physiotherapists to care for. The results of this and previous studies support the use of the fentanyl ITS as an alternative to morphine PCIA.

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