Postoperative Pain Control with a New Transdermal Fentanyl Delivery System

A Multicenter Trial

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Background: A new transdermal delivery system for fentanyl is available in two strengths: 7.0 to 80 and 90 to 100 
μg·kg⁻¹·h⁻¹ (40- and 60-cm² patches, respectively). Their short onset and 24-h drug delivery make them attractive for postoperative pain control.

Methods: Both doses of the new transdermal fentanyl patches were evaluated for the relief of postoperative pain in 145 patients after gynecologic exploratory laparotomy. The study was conducted at four centers using a prospective, randomized, placebo-controlled, double-blind format. Patients were randomly assigned to one of three study groups: group 1 patients received two placebo patches; group 2 patients received a 40-cm² fentanyl patch and a 60-cm² placebo patch; and group 3 patients received a 60-cm² fentanyl patch and a 40-cm² placebo patch. Patient-controlled morphine use and pain, sedation, and comfort scores were assessed postoperatively every 4 h for 36 h after patch placement.

Results: Patients' assessment of their analgesia was significantly (P < 0.05) better in group 2 at 16 and 24 h and in group 3 at 8, 12, 16, 20, and 24 h postoperatively, compared with the patients in group 1. Patients in groups 2 and 3 required less supplemental morphine to maintain satisfactory analgesia than did the patients in group 1. Patients in groups 2 and 3 had greater incidences of pruritus, erythema, and respiratory depression than did those receiving placebo.

Conclusions: Concern exists regarding the side effects of this new transdermal fentanyl patch. Therefore, this new patch will need further research before it can be recommended as an adjunct in controlling postoperative pain. (Key words: Analgesics, opioids; fentanyl. Anesthetic techniques: transdermal delivery.)

THE control of postoperative pain has led to the development of increasingly invasive techniques. The use of opioids by the spinal route and intrathecal analgesia are two invasive modalities commonly used for the relief of postoperative pain.1,2 These techniques have inherent risks (bleeding, infection, and pneumothorax) as well as risks related to the medication (pruritus, nausea, respiratory depression, and local anesthetic toxicity). The development of an effective, noninvasive, continuous analgesia delivery system would be an attractive alternative for the control of postoperative pain. Patient-controlled analgesia has been useful in that regard, but may provide inadequate analgesia during periods of extended sleep, requires the use of mechanical pumps and is an invasive technique.

Michaels et al.3 were the first to describe the possibility of transdermal drug delivery. Transdermal administration of a variety of medications including nitroglycerin, clonidine, and scopolamine have been reported. Transdermal administration results in consistent, stable concentrations of these medications in plasma. Transdermal fentanyl, originally described by Sebel et al. in 1987,4 is the first opioid commercially available for transdermal delivery (Duragesic, Janssen

Materials and Methods

As part of a multicenter study, patients scheduled for gynecologic surgery were enrolled in the study by each institution's Scientific and Institutional Review Committee. Patients who had a history of drug abuse, body weight <90 kg, or who were older than 65 years were excluded from the study.

The study was carried out at four centers using a double-blind, placebo-controlled, multicenter study. Each patient received either a 40- or 60-cm² patch. The 40-cm² patch contained 40 μg·h⁻¹ fentanyl (TEP-40) and the 60-cm² patch contained 60 μg·h⁻¹ fentanyl (TEP-60). The patches were applied to the chosen area, usually the lower back or inner thigh, and were removed after 24 h.

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Anesthesiology, V 83, No 3, Sep 1995

Anesthesiology, V 83, No 3, Sep 1995
TRANSDERMAL FENTANYL

Pharmaceutica, Piscataway, NJ). The Food and Drug Administration has limited approval for its use in patients with chronic cancer pain.

Because the Duragesic patch has a slow onset and long duration, the development of a patch with a faster onset and shorter duration of action would be more attractive for the control of postoperative pain.

The purpose of this study was to determine the efficacy and side effects profile of a new transdermal fentanyl delivery system (TDFF-40 and -60, Anaquest, Liberty Corner, NJ) in controlling postoperative pain in female patients undergoing lower abdominal gynecologic surgery.

Materials and Methods

As part of a multicenter study, 144 women who were scheduled for gynecologic exploratory laparotomy were enrolled in the study. The protocol was approved by each institution’s Scientific Review Board and written informed consent was obtained from each patient. Patients who had a history of recent opioid therapy or drug abuse, body weight exceeding 110 kg, or American Society of Anesthesiologists physical status 3 or greater or who were older than 65 yr were excluded from the study.

The study was carried out in a prospective, randomized, double-blind, placebo-controlled fashion using three study groups. Each patient received two patches (40 and 60 cm²) placed on the upper torso, approximately 1 h before operation. The patients in group 1 received a 40- and a 60-cm² placebo patch. Patients in group 2 received a 40-cm² transdermal fentanyl patch (TDFF-40) and a 60-cm² placebo patch. Patients in group 3 received a 60-cm² transdermal fentanyl patch (TDFF-60) and a 40-cm² placebo patch. All patches remained in place for 24 h. One square centimeter of the active patch contained 0.16 mg fentanyl. All active patches were of the same composition per square centimeter; therefore, the delivered dose was determined by the size (area) of the patch. After placement of the patches, patients received either diazepam 0.1 mg/kg orally, or midazolam 0.035 mg/kg intramuscularly. Baseline values for blood pressure, heart rate, respiratory rate, and hemoglobin oxygen saturation by pulse oximetry (SpO₂) were recorded.

Anesthetic technique was standardized for all patients as follows. Induction of anesthesia was achieved with sodium thiopental or thiamylal sodium, 1–5 mg/kg intravenously. Succinylcholine, 1.5 mg/kg intravenously, was used to facilitate tracheal intubation. Fentanyl was given to a total of 5 µg/kg intravenously. Maintenance of anesthesia was achieved with N₂O-O₂ in a 3:2 ratio. Isoflurane was added as dictated by patient need, to as much as 1.3% end-tidal concentration. Intravenous vecuronium, 0.05 mg/kg initially followed by 0.01 mg/kg when needed, was used to maintain neuromuscular blockade. Intravenous neostigmine and glycopyrrolate were used for reversal of residual neuromuscular blockade.

Upon arrival to the postanesthesia care unit (PACU), patients were given morphine sulfate 110–150 µg/kg intravenously followed by an on-demand dose of 20–40 µg/kg intravenously with a 10-min lockout from a patient-controlled pump for supplemental analgesia. A maintenance infusion of morphine was not administered. Total cumulative morphine administered in the first 24 h postoperatively was recorded by a research assistant.

Patients were evaluated by a research assistant who was not a member of the anesthetizing team, upon entry into the PACU and at 10, 15, 30, and 60 min thereafter. Blood pressure, respiratory rate, SpO₂, and pulse rate were recorded. Comfort and sedation scores were recorded (Table 1).

All patients were continuously monitored by an observer for the entire time the patch was in place. All of the aforementioned variables were recorded at 2-h intervals for the first 12 h postoperatively, and then at 4-h intervals for the next 24 h. At these same times patients completed a global self-assessment of analgesia by answering the question: “How do you rate your pain relief?” Their response was graded on a scale of 0–3.

Anesthesiology, V 83, No 5, Sep 1995


Table 1. Comfort and Sedation Scoring System

<table>
<thead>
<tr>
<th>Comfort</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = asleep</td>
<td>1 = asleep</td>
</tr>
<tr>
<td>2 = no discomfort</td>
<td>2 = alert</td>
</tr>
<tr>
<td>3 = mild discomfort</td>
<td>3 = drowsy, oriented, initiates conversation</td>
</tr>
<tr>
<td>4 = moderately uncomfortable</td>
<td>4 = drowsy, oriented, does not initiate conversation</td>
</tr>
<tr>
<td>5 = very uncomfortable</td>
<td>5 = very drowsy, disoriented, does not initiate conversation</td>
</tr>
<tr>
<td>6 = severely uncomfortable</td>
<td>6 = stuporous</td>
</tr>
</tbody>
</table>

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Table 2. Pain Relief Scoring Systems

<table>
<thead>
<tr>
<th>Global self-assessment of analgesia</th>
<th>Visual analog scale (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = excellent relief, no pain</td>
<td>0–100 mm (0 = no pain, 100 = worst pain imaginable)</td>
</tr>
<tr>
<td>1 = good relief, mild pain</td>
<td></td>
</tr>
<tr>
<td>2 = marginal relief, moderate pain with requests for supplemental analgesia</td>
<td></td>
</tr>
<tr>
<td>3 = Poor relief, severe pain with excessive requests for supplemental analgesia</td>
<td></td>
</tr>
</tbody>
</table>

Visual linear analogue scale (VAS) scores (0–100 mm) were also used to assess pain relief.

All patches were removed 24 h after application. Patients were continuously monitored by the observer for an additional 12 h for erythema or edema at the patch site (scale of 0–4, where 0 = none, 4 = severe) at 4, 8, and 12 h after patch removal, and for nausea, vomiting, pruritus and respiratory depression (i.e., respiratory rate < 8 breaths/min or SpO₂ < 90%) at the same times.

Plasma fentanyl concentrations were measured before patch placement, upon the patient’s arrival in the PACU, and 12 and 24 h after patch placement. Blood was placed on ice and, within 1 h of collection, was centrifuged and the plasma frozen at −20°C. Plasma was analyzed by radioimmunoassay to determine fentanyl concentration with a lower limit of sensitivity of 0.05 ng/ml. Fentanyl assays were performed at Harris Laboratories (Lincoln, NE).

Statistical Methods

Parametric data (age, weight, morphine sulfate dosage, SpO₂, VAS scores, intraoperative fentanyl total dose, plasma fentanyl concentrations) were compared using an analysis of variance (between groups design). When \( P \leq 0.05 \), a post hoc analysis was performed with Scheffe’s test to identify specific differences.

Nonparametric data (sedation, comfort, and analgesia) were compared using Kruskal-Wallis analysis of variance by ranks. When \( P \leq 0.05 \), Bonferroni’s correction to the Mann-Whitney rank sum test was used to distinguish differences between groups. Intergroup incidence of respiratory depression was evaluated with Fisher’s exact test. A \( P \) value of \( \leq 0.05 \) was considered statistically significant.

Results

One hundred forty-three patients were studied (45 in group 1, 49 in group 2, and 49 in group 3). One patient with a history of asthma had severe bronchospasm in the immediate postoperative period and was withdrawn from the study. There were no differences among the groups with respect to mean age, mean weight, or ASA physical status (table 3).

All patients arrived at the PACU within 3–6 h after patch placement. The patients in group 1 demonstrated significantly lower plasma fentanyl concentration upon arrival to the PACU (95% confidence interval [CI], –0.8 to –0.05) at 12 h (95% CI, –2.1 to 1.3) and at 24 h (95% CI, –2.0 to –1.4) after patch placement compared with the patients in group 3 (fig. 1). Group 2 patients demonstrated higher plasma fentanyl concentrations than the patients in group 1 at 12 (95% CI, –1.4 to –0.8) and 24 h (95% CI, –1.5 to –1.0) after patch placement. No statistical differences in mean concentrations in groups 2 and 3 were noted. Supplemental intravenous opioids were administered in 2 of the 5 patients in group 2 and 3 of the 5 patients in group 3. No patients required additional patch placement. No statistical differences in mean concentrations in groups 2 and 3 were noted. Supplemental intravenous opioids were administered in 2 of the 5 patients in group 2 and 3 of the 5 patients in group 3. No patients required additional patch placement. No statistical differences in mean concentrations in groups 2 and 3 were noted. Supplemental intravenous opioids were administered in 2 of the 5 patients in group 2 and 3 of the 5 patients in group 3. No patients required additional patch placement.
TRANSDERMAL FENTANYL

Fig. 2. Supplemental intravenous morphine received by the patients through their patient-controlled analgesia device. A significant opioid-sparing effect was seen in patients receiving active patches. Values are expressed as mean ± SD. *P < 0.001 compared with group 1; #P < 0.01 compared with group 1.

Fig. 3. The visual analogue scale scores reported by the patients in the high-dose patch group were significantly lower 8, 10, 16, and 20 h after patch placement compared with the patients receiving placebo and those receiving low-dose patches. Values are expressed as mean ± SD. *P < 0.05 compared with groups 1 and 2.

Fig. 4. Patient self-assessment of analgesia demonstrates improved pain relief by the patients with a high-dose patch in five of ten assessment periods compared with placebo. Patients with a low-dose patch reported a difference in one of ten assessment periods compared with placebo. Values are expressed as median (and range). *P < 0.001 compared with group 1; #P < 0.001 compared with group 1; ++P < 0.01 compared with group 1; ++P < 0.05 compared with group 1.
Table 4. Side Effects

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Pruritus</th>
<th>Erythema</th>
<th>Respiratory Depression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 45)</td>
<td>21 (47)</td>
<td>10 (22)</td>
<td>4 (8)</td>
<td>6 (13)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>2 (n = 49)</td>
<td>26 (53)</td>
<td>8 (16)</td>
<td>3 (6)</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>3 (n = 49)</td>
<td>33 (67)</td>
<td>9 (18)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Values are number of patients who experienced side effects. Values in parentheses are number of patients who experienced side effects expressed as a percentage of total in that group. Values in brackets represent number of patients who required treatment.

* Respiratory depression is defined as patients demonstrating persistent SpO₂ values <90% or respiratory rate >0 breaths/min.
† P = 0.05 versus Groups 1 and 3.
‡ P = 0.05 versus Group 1.

quent in the patients in group 3 compared with the patients in group 1 (table 4). The characteristics of all patients in whom respiratory depression developed are presented in table 5. Two patients in group 1 (placebo) had respiratory depression, and one of these required mechanical ventilation in the PACU. This patient had a plasma fentanyl concentration of 0.48 ng/ml on arrival to the PACU. Three patients in group 2 and eight in group 3 had respiratory depression. Four of these patients (two in group 2 and four in group 3) required intravenous naloxone and four had their patches removed (all in group 3). There were no differences between the patients who received fentanyl patches and had respiratory depression and the others who received fentanyl patches but did not have respiratory depression with respect to age, ASA physical status, amount of intraoperative fentanyl used or plasma fentanyl concentrations. Compared with patients who did not have respiratory depression, patients who had respiratory depression weighed less and had higher plasma fentanyl concentrations upon arrival to the PACU (table 6). Respiratory depression occurred at 24 h in all three patients in group 2. However, in the patients in group 3, respiratory depression occurred within 8 h in five patients and in only three patients thereafter.

Discussion

The patches used in the current study were developed with the more rapid attainment of stable analgesia as a goal. The TDPPs that we studied contain a supply of fentanyl in a saturated matrix weave, a backing, and a release liner. Propylene glycol monolaurate is added to facilitate fentanyl dispersion in the adhesive. After removal of the release liner and application to the skin, the flow of fentanyl into the body is controlled by the skin and surface contact area, without a rate-controlling membrane, in contrast with the ethylene copolymer membrane and reservoir of the longer-term patch (Duragesic). The absence of a rate-limiting adhesive membrane is primarily responsible for the rapid onset obtained with the Anaquest TDFP product.

Mean concentrations in plasma (± SD) of 1.34 ± 0.94 ng/ml were achieved with TDFP-40 and 1.98 ± 1.30 ng/ml with the TDFP-60 at 12 h after patch application. At 24 h, concentrations were 1.48 ± 0.70 ng/ml with TDFP-40 and 1.90 ± 1.00 ng/ml with TDFP-60. Therapeutic fentanyl concentrations were achieved 3–6 h after patch placement and significant differences between patients in group 3 and those in the placebo group were seen on arrival to the PACU. Despite fentanyl use intraoperatively, decay in plasma fentanyl concentration was significantly more rapid in the patients in group 1 compared with the patients in group 3 by the time of PACU arrival and compared with both active patch groups by 12 and 24 h. The biopharmaceutics of the patch are described in an accompanying article.7

In contrast, the currently available patches (i.e., Duragesic) have demonstrated prolonged times until development of steady-state concentrations in plasma.9,10 Furthermore, the time required for a 50% decrease in plasma fentanyl concentration after patch removal is approximately 16 h.9,10 These qualities make the Duragesic patch less convenient for the relatively short-term analgesia usually required postoperatively. Attempts to use the Duragesic patch postoperatively have yielded mixed results.11–13 On January 17, 1994, Janssen Pharmaceutica issued a letter to health care professionals to reinforce precautions for safe use and to alert them to revised product labeling, including its contraindication for use in acute or postoperative pain.14

Continuously administered fentanyl has been widely used for the control of postoperative pain by a variety of routes.14,15 Transdermal fentanyl delivery systems should deliver and maintain stable concentrations in plasma within the therapeutic range. The relation between plasma fentanyl concentration and analgesia has been established. A plasma fentanyl concentration of 0.23–1.18 ng/ml offers analgesia with a minimum effective concentration (MEC) of


Anesthesiology, V 83, No 3, Sep 1995
Table 5. Data of Patients Developing Respiratory Depression

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>IOF (µg)</th>
<th>Tm RD (h)</th>
<th>Fentanyl Plasma (ng/ml)</th>
<th>12 h PPP</th>
<th>24 h PPP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Arrival</td>
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</tr>
<tr>
<td>1</td>
<td>65</td>
<td>102</td>
<td>400</td>
<td>8</td>
<td>0</td>
<td>1.1</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>63</td>
<td>200</td>
<td>24</td>
<td>0.3</td>
<td>1.8</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>54</td>
<td>150</td>
<td>24</td>
<td>0.1</td>
<td>1.2</td>
<td>2.4</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>57</td>
<td>250</td>
<td>24</td>
<td>0.1</td>
<td>1.9</td>
<td>1.4</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>68</td>
<td>300</td>
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<td>5.8</td>
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</tr>
<tr>
<td>3</td>
<td>46</td>
<td>54</td>
<td>250</td>
<td>8</td>
<td>0.1</td>
<td>2.8</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>64</td>
<td>250</td>
<td>8</td>
<td>0.1</td>
<td>2.0</td>
<td>1.3</td>
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<tr>
<td>3</td>
<td>48</td>
<td>49</td>
<td>200</td>
<td>6</td>
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<td>0.7</td>
<td>2.9</td>
<td>1.5</td>
</tr>
<tr>
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<td>64</td>
<td>67</td>
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</tr>
<tr>
<td>3</td>
<td>37</td>
<td>49</td>
<td>100</td>
<td>24</td>
<td>0.2</td>
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<td>3.8</td>
</tr>
<tr>
<td>3</td>
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<td>8</td>
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<td>5.6</td>
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<td>200</td>
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<td>0.1</td>
<td>0.7</td>
<td>1.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

IOF = intraoperative fentanyl use; Tm RD = Time of respiratory depression postpatch placement; PPP = postpatch placement; — = plasma samples were not drawn.

0.63 ng/ml for abdominal operations. MEC is defined as the minimum concentration that produces consistent and constant pain relief if the blood opioid concentration is maintained in excess of the MEC value. Gourlay et al. determined the MEC for fentanyl in patients undergoing abdominal operations by assaying blood samples taken immediately before patient requests for more pain medication. Plasma fentanyl concentrations greater than 2 ng/ml have been shown to cause a higher incidence of side ef-

Table 6. Comparative Data of Patients Receiving Active Patches with and without Respiratory Depression

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>IOF (µg)</th>
<th>Total MSO₂ (mg/24 h)</th>
<th>Plasma Fentanyl Concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>RD (n = 11)</td>
<td>49 ± 13</td>
<td>59 ± 7*</td>
<td>223 ± 61</td>
<td>22 ± 17</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>NRD (n = 83)</td>
<td>42 ± 18</td>
<td>72 ± 16</td>
<td>243 ± 100</td>
<td>28 ± 27</td>
<td>0.09 ± 0.06</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
RD = patients who developed respiratory depression; NRD = patients who did not develop respiratory depression; MSO₂ = morphine sulphate; IOF = intraoperative fentanyl total dose; PPP = postpatch placement.
*P ≤ 0.05 versus patients who did not develop respiratory depression.
fecteds. It is not surprising that there is such a wide range of analgesic concentrations in plasma, because analgesic requirements are influenced by pharmacokinetics and pharmacodynamics, as well as by psychological and gender factors.

A similar incidence of adverse events was reported in the three groups with the exception of pruritus, erythema, and respiratory depression. Although pruritus was reported more frequently in the active patch groups, the severity of itching was relatively mild and rarely required intervention. Localized erythema at the patch site was reported more frequently in patients receiving the TDFP-40 (low-dose) patch than in those receiving a placebo or TDFP-60 (high-dose) patch. This may indicate that other factors, such as patient sensitivity or hydration status, are more significant for the development of local irritation than the fentanyl in the patch. The incidence of nausea and vomiting was not different among the groups and was comparable to that reported elsewhere.10-12

Respiratory depression was more common in the active patch groups. Although respiratory depression developed in two patients in the placebo group, its occurrence in the PACU with a documented therapeutic plasma fentanyl concentration indicates its probable relation to intraoperative fentanyl administration. In three patients in group 2 respiratory depression developed approximately 24 h after patch placement. This 6% incidence compares favorably with the recent report by Sevarino et al.13 who found incidences of 6% and 9% of respiratory depression (defined in her study as respiratory rate < 8 breaths/min) with significantly lower-dose fentanyl patches (25 and 50 μg/h, respectively). Respiratory depression developed in eight patients (16%) in group 3, but in five of those (63%) it occurred during the early postoperative period. It is during this early postoperative phase that intraoperative fentanyl use could have contributed to its occurrence. This is supported by finding significantly higher plasma fentanyl concentrations in the PACU in patients in whom respiratory depression developed compared with those in whom it did not. Decreasing or eliminating intraoperative opioid administration entirely could conceivably decrease the incidence of respiratory depression. However, concern may exist that inadequate pain relief in the immediate postoperative period may occur. The achievement of rapid (i.e., 3−4 h after patch placement), therapeutic plasma fentanyl concentrations, as seen with TDFP-40 and TDFP-60, may reduce this concern. However, even when no other opioids are given, respiratory depression can occur. In the accompanying article on the biopharmaceutics of patch administration,7 the TDFP-60 patch was prematurely removed from 2 of 14 subjects because of significant respiratory depression. Plasma fentanyl concentrations at time of patch removal were 2.9 and 3.22 ng/ml.

Improved postoperative analgesia was found in patients who received active patches. A difference in VAS pain scores was not found more often because of the patients’ ability to dose themselves with morphine. The ability of the patients to autoadminister morphine to achieve acceptable pain relief resulted in finding significant differences in pain relief only occasionally. The significant morphine-sparing effect of the active patches underscores their effectiveness in the relief of postoperative pain.

In summary, a new transdermal fentanyl delivery system was investigated in patients undergoing abdominal gynecologic operations to determine its safety and efficacy for postoperative pain management. Patients who received active patches reported lower VAS pain scores and required less supplemental morphine to provide adequate analgesia compared with patients who received placebo patches. The new fentanyl patch shows promise as an adjunct in the control of postoperative pain. As with any continuous drug delivery system, limitations of the patch include the inability to titrate dosage. Although use of the patch resulted in a decrease in supplemental morphine use and better pain control, this potential benefit was accompanied by significantly increased plasma fentanyl concentrations and an increased incidence of respiratory depression. The high-dose (60-cm²) patch and possibly the low-dose (40-cm²) patch appear to be excessive for use in postoperative pain management. Further research will be needed to determine whether a safe and effective patch dose can be found and to determine the influence of the intraoperative anaesthetic technique on the side effects profile.

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References
TRANSDERMAL FENTANYL

References