PriCara,
Unit of Ortho-McNeil, Inc.

Clinical Study Report

Comparison of the Safety and Efficacy of Patient Controlled Analgesia Delivered by Fentanyl HCl Transdermal System Versus Morphine IV Pump for Pain Management after Primary Unilateral Total Hip Replacement

Protocol CAPSS-319; Phase IIIb

PRINCIPAL INVESTIGATOR:
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DATE STUDY INITIATED: 30 March 2004

DATE STUDY COMPLETED: 2 April 2005

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

SYNOPSIS

NAME OF SPONSOR/COMPANY: PriCara, Unit of Ortho-McNeil, Inc. **NAME OF FINISHED PRODUCT:** E-TRANS® (fentanyl HCl) system **NAME OF ACTIVE INGREDIENT(S):** Fentanyl HCl	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Protocol No.: CAPSS-319 **Title of Study:** Comparison of the Safety and Efficacy of Patient Controlled Analgesia Delivered by Fentanyl HCl Transdermal System Versus Morphine IV Pump for Pain Management after Primary Unilateral Total Hip Replacement		
Principal Investigator: Craig Hartrick, M.D. - William Beaumont Hospital, Royal Oak, Michigan; USA		
Publication (Reference): None		
Study Initiation/Completion Dates: 30 March 2004 / 2 April 2005		**Phase of development:** IIIb
Objectives: The primary objective of this study was to compare the safety and efficacy of E-TRANS® fentanyl treatment versus IV PCA morphine treatment for the management of post-operative pain in patients who had undergone primary unilateral total hip replacement. Additional objectives were to assess the safety of the E-TRANS® fentanyl system for pain management in this surgical population and to compare the clinical utility of the E-TRANS® fentanyl system to IV PCA morphine.		
Methodology: This was a multicenter, open-label, randomized, comparative, parallel treatment study. The study consisted of a screening phase followed by randomization into an open-label treatment phase. The screening phase began up to 21 days prior to surgery and the treatment phase began while the patient was in the post-anesthesia care unit/recovery room (PACU) following surgery. Following surgery patients were randomized into 1 of 2 treatment groups to receive E-TRANS® fentanyl or IV PCA morphine. The patients randomized to E-TRANS® received fentanyl 40 micrograms (μg) per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 μg/hour) or a maximum of 80 doses (3.2 milligrams [mg]) with each device. Each E TRANS® fentanyl system would inactivate when 80 doses were used or 24 hours elapsed after the first dose. If necessary, patients received a new system to complete the 24-hour treatment period if 80 doses were used. Patients randomized to receive IV PCA morphine received 1 mg morphine bolus doses with a lockout period of 5 minutes, up to 10 doses/hour (10 mg/hour) to a maximum of 240 doses/24 hours (240 mg/24 hours). Patients were permitted rescue medication as needed (p.r.n.) for re-titration to comfort during the first 3 hours after study medication had been initiated. Patients randomized to E-TRANS® fentanyl were to receive fentanyl IV and patients randomized to IV PCA morphine were to receive IV morphine rescue medication. If administration of the specified rescue medication was not possible, the patient was permitted to receive either morphine or fentanyl. The dosage and frequency was to be in accordance with standard practice at each study site. Patients were permitted to be transitioned to oral analgesics at any time after Hour 0 as per the institution's standard practice; however, transition to oral analgesics was <u>not</u> to begin while the patient was still wearing the E-TRANS® fentanyl system or while the IV PCA morphine device was enabled. The open-label treatment phase lasted up to 72 hours. At the end of the 72 hours or upon completion of final study		

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procedures, patients in the E-TRANS® fentanyl group had their last device removed and their analgesic regimen prescribed by their physician. Patients in the IV PCA morphine group completed final study procedures and either continued IV PCA morphine or received another analgesic regimen according to the standard of care at that institution.

Prior to the recall of Vioxx® (rofecoxib) on September 30, 2004, all patients were to receive Vioxx® 25 mg 2 to 4 hours prior to surgery and 25 mg each day of the study. The use of other non-steroidal anti-inflammatory drugs (NSAIDs) intra-operatively and during the post-operative screening and treatment periods were prohibited. After September 30, 2004, the use of NSAIDs or cyclooxygenase Type II (COX-2) inhibitors intraoperatively during the post-operative screening and treatment periods was prohibited.

Number of Patients (planned and analyzed): The study was planned for 50 centers in the United States (US). Each center was expected to enroll approximately 16 patients for a total of approximately 800 treated patients. Fifty-two centers in the US enrolled a total of 799 patients for this study.

Diagnosis and Main Criteria for Inclusion: Patients were post-operative men and women, 18 years of age and older who had primary unilateral hip replacement and who had been titrated with IV opioids as clinically appropriate, and reported their pain was ≤4 on an 11-point scale and stated they were comfortable for at least 30 minutes in the PACU.

Test Product, Dose and Mode of Administration, Batch No.: Patients randomized to E-TRANS® (fentanyl) received 40 micrograms (μg) fentanyl per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 μg/hour) or a maximum of 80 doses (3.2 mg) with each device (batch numbers 0330669 and 0430235).

Reference Therapy, Dose and Mode of Administration, Batch No.: Morphine sulfate solution, 1 mg/mL, infused intravenously by a PCA pump set for 1-mg bolus doses with a lockout period of 5 minutes and a maximum hourly dosage of 10 mg/hr (maximum of 240 doses/24 hours [240 mg/24 hours]). The study sites supplied both the morphine solution and the PCA pump.

Duration of Treatment: The study consists of a screening phase (up to 21 days prior to surgery) followed by randomization into an open-label treatment phase, which lasted up to 72 hours.

Criteria for Evaluation:

Efficacy: Patient Global Assessments (PGA) of method of pain control were completed 24, 48 and 72 hours after treatment was initiated or at study completion/termination. Patients were also assessed periodically during study treatment for pain intensity. Outcome measures related to Ease-of-Care were assessed by patients at 72 hours or at study completion/termination and by the physical therapist after each therapy session. After all patients completed the study at each individual site, the Nurse Ease-of-Care Questionnaires were completed by floor nurses and research nurses who provided primary care for patients participating in this study. The investigator and/or the surgeon were to complete a global assessment of method of pain control after each patient completed participation. Adherence of E-TRANS® fentanyl systems and the number of on-demand doses were recorded. Information regarding the type and amount of analgesics prescribed for the patient at study completion/termination, the date and time of ambulation, eligibility for discharge and actual hospital discharge were recorded.

SYNOPSIS (CONTINUED)

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The reason for discontinuation for each patient who did not complete the study was collected and the proportion of patients who discontinued for insufficient pain relief was tabulated. Data regarding non-routine events were also collected.

Clinical Use: The Patient Ease-of-Care Questionnaire, Pain Management Goal, Nurse Ease-of-Care Questionnaire, Physical Therapist Ease-of-Care Questionnaire, Assessment of the Adherence of the E-TRANS® fentanyl system, Non-Routine Events Checklist, Post-Study Analgesics, Time to Ambulation, Time to Discharge, and a Brief Pain Inventory were also assessed to evaluate clinical use of both treatment groups.

Safety: Safety evaluations included oxygen saturation, vital signs (temperature, heart rate, respiratory rate, and blood pressure), topical and systemic adverse events, and the Ramsay Sedation Scale. A physical examination and pregnancy test were also performed during screening. The pregnancy test was required for women of child-bearing potential only if one had not been done 3 days prior to surgery.

Statistical Methods: Efficacy parameters were analyzed for both ITT and evaluable patients. Two-sided 95% confidence intervals for treatment difference were constructed to evaluate the equivalence of the 2 treatments for the main efficacy outcomes.

The primary efficacy outcome was success in the PGA of method of pain control at the 24-hour time point in the evaluable for efficacy population (defined as all randomized patients who received at least 3 hours of treatment with E-TRANS® fentanyl or IV PCA morphine). Success was defined as a response of good or excellent on the PGA of method of pain control. For patients who discontinued before 24 hours, the primary efficacy outcome was defined as success at the final PGA questionnaire obtained at the time of discontinuation.

The statistical objective of the study was to establish that the proportion of successes based on the 24-hour PGA for E-TRANS® fentanyl was equivalent to that for IV PCA morphine. E-TRANS® fentanyl and IV PCA morphine were declared equivalent as methods of pain control if the 2-sided 95% confidence interval (CI) for the difference between treatments in the proportion of successes at 24 hours based on the evaluable for efficacy population fell within the interval from -10% to 10%.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY, CLINICAL UTILITY, AND EASE-OF-CARE RESULTS:

Efficacy Results:

For the primary efficacy variable:

- Equivalence was demonstrated by achieving similar success (excellent and good) rates for the method of pain control based on the first 24-hour PGA for the E-TRANS® fentanyl group (83.8% [326/389]) and IV PCA morphine group (83.4% [331/397]), 95% CI = -4.7%, 5.6%.

The secondary efficacy variables showed results similar to the primary efficacy variable:

- The E-TRANS® fentanyl group (84.8% [330/389]) achieved a similar success rate for the last PGA compared with the IV PCA morphine group (87.2% [346/397]), 95% CI = -7.2%, 2.5%.
- The E-TRANS® fentanyl and IV PCA morphine groups rated their method of pain control similarly based on the 48-hour and 72-hour PGA, although the E-TRANS® fentanyl group success rating tended to be slightly higher than IV PCA morphine.
- Equivalence was shown in the first 24 hours mean last pain intensity score.(2.9) (difference = 0, 95% CI = -0.33, 0.32).
- The IGA and SurGA showed E-TRANS® fentanyl and IV PCA morphine groups were similar in method of pain control rating, although the E-TRANS® fentanyl group tended to be slightly higher than IV PCA morphine group.
- The proportions of dropouts for any reason were similar for the E-TRANS® fentanyl group (14.4% [56/389]) compared with the IV PCA morphine group (12.6% [50/397]; $P = 0.460$). There were more dropouts due to inadequate analgesia for the E-TRANS® fentanyl group (10.5% [41/389]) compared with the IV PCA morphine group (5.0% [20/397]) and the difference was statistically significant, $P = 0.0039$.
- Subgroup analyses showed both older (>65 years) and younger (<65 years) patients rated their method of pain control the same for E-TRANS® fentanyl and IV PCA morphine. Subgroups of race and BMI ≥ 40 kg/m^2 were considered too small to draw any meaningful conclusions.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY, CLINICAL UTILITY, AND EASE-OF-CARE RESULTS (Continued):

Clinical Utility Results:

- The E-TRANS® fentanyl and IV PCA morphine groups were similar in the number of IV line problems, the number of steps ambulated, the time to ambulation, the time to eligibility for hospital discharge, the time to actual hospital discharge, and the disposition at time to discharge.
- The E-TRANS® fentanyl and IV PCA morphine groups had a similar incidence of non-routine events and post-treatment analgesic use.
- The E-TRANS® fentanyl system was similar to the IV PCA morphine pump in the number of suspected technical failures.

Ease-of-Care Results:

- Patients, their physical therapists and nurses rated the E-TRANS® fentanyl system easier to use with higher satisfaction than IV PCA morphine.

Efficacy Summary:

- The E-TRANS® fentanyl system was similar to IV PCA morphine for the management of acute post-operative pain requiring opioids in a medically supervised setting for up to 3 days in duration.
  - Results of the analyses for the ITT population were not different in any outcomes compared to analyses conducted for the efficacy evaluable population.
  - There were no clinically important differences shown for patients in either treatment group with Vioxx® intended use compared with patients without Vioxx® intended use. Equivalence based on ratings of success (excellent and good) of PGA for the first 24-hours and mean last pain intensity score in the first 24 hours were not effected by Vioxx® intended use.

SAFETY RESULTS:

- The most common systemic adverse event that was likely related to opioid therapy in both the E-TRANS® fentanyl and IV PCA morphine groups was nausea. Insomnia, dizziness and constipation were higher in the E-TRANS® fentanyl group and nausea, vomiting, hypotension, pruritus, urinary retention, tachycardia, somnolence, confusion, and oliguria were higher in the IV PCA morphine group.
- Adverse events related to the respiratory system were similar in both treatment groups (9.6% in E-TRANS® fentanyl and 11.1% in IV PCA morphine). The most common treatment-emergent respiratory adverse event was hypoxia. (5.8% in the E-TRANS® fentanyl and 6.9% in the IV PCA morphine).

SYNOPSIS (CONTINUED)

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SAFETY RESULTS (Continued):

- Adverse events related to the central nervous system were similar in both treatment groups (18.5% in E-TRANS® fentanyl and 17.1% in IV PCA morphine). The most frequent treatment-emergent nervous system adverse event was insomnia (6.6% in E-TRANS® fentanyl group and 5.4% in IV PCA morphine group). The treatment-related nervous system adverse events of dizziness and insomnia were higher in the E-TRANS® fentanyl group, while somnolence and confusion were higher in the IV PCA morphine group.
- Adverse events related to the cardiovascular system were higher in the IV PCA morphine group (13.4% in E-TRANS® fentanyl and 18.8% in IV PCA morphine). The most frequent treatment-emergent cardiovascular system adverse event was hypotension (7.3% in E-TRANS® fentanyl group and 12.1% in IV PCA morphine group). The incidence of the treatment-related event of hypotension was higher in the IV PCA morphine group (8.2%) as compared to the E-TRANS® fentanyl group (4.6%).
- Application Site Reactions:
  - For E-Trans® fentanyl the following events were reported: dry and flaky skin, erythema, itching, pain, vesicles and other; and
  - For IV PCA morphine the following event was reported: infusion site reactions.
- Adverse events that were judged to be probably related, possibly related or had an unknown relationship to study treatment were recorded in 43.0% of patients in the ITT population who received E-TRANS® fentanyl and 52.7% of patients who received IV PCA morphine.
- 18 patients in the E-TRANS® fentanyl group and 18 in the IV PCA morphine group, experienced serious adverse events. Of these 36 patients, 3 patients in the E-TRANS® fentanyl group and 6 patients in the IV PCA morphine group had serious adverse events that were considered related to study medication. Two patients experienced clinically relevant respiratory depression, and both were in the IV PCA morphine group. One patient died due to a massive myocardial infarction that was unrelated to study treatment with IV PCA morphine.
- There were 48 treatment-emergent adverse events leading to early study termination. Of these 6/14 (42.9%) treatment-emergent adverse events in the E-TRANS® fentanyl group and 27/34 (79.4%) treatment-emergent adverse events in the IV PCA morphine group were considered treatment-related.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS (Continued):

- In evaluating sedation, patients in the E-TRANS® fentanyl group scored lower at more scheduled assessments compared with patients in the IV PCA morphine group. The majority of patients in both treatment groups scored a "2" (cooperative, oriented and tranquil) for their worst post-baseline score.(E-TRANS® fentanyl group: 71.4%,IV PCA morphine group: 74.3%).
- There were no clinically meaningful differences in the type or frequency of adverse events for the With-Vioxx® and Without-Vioxx® intended use populations.

SUMMARY – CONCLUSIONS

The E-TRANS® fentanyl system is a similar analgesic to IV PCA morphine and is as acceptable to patients as IV PCA morphine for the management of acute post-operative pain for up to 3 days in duration.

Date of the report: 29 August 2005

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