Title: TRANSDERMALLY ADMINISTERED FENTANYL FOR POSTOPERATIVE PAIN: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

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Introduction: New strategies for management of postoperative pain have focused on continuous or very frequent (e.g. patient controlled analgesia) administration of analgesics in an effort to provide relatively constant levels of drug and thereby achieve prolonged analgesia. Percutaneous (transdermal) administration of drugs is a non-invasive method which often provides relatively stable concentrations of drug in the body over extended periods of time. The synthetic opioid analgesic fentanyl (F) has been incorporated into a transdermal therapeutic system (TTS[1]); we report the preliminary results of a controlled study of the TTS (fentanyl) in postoperative pain.

Methods: The study protocol was approved by the Human Subjects Committee. Written informed consent was obtained. 43 patients (pts) of either sex between the ages of 18 and 70 yrs undergoing orthopedic or abdominal surgical procedures under general anesthesia were enrolled. Pts of ASA classification IV or V were excluded, as were pts with narcotic exposure in excess of 20 mg of parenteral morphine or equivalent for 7 or more days prior to enrollment. The TTS (nominal delivery rate= 75 ug F/hr) was placed on the anterior upper thorax of each pt approximately 2 hr preoperatively. The TTS was to remain in place for a total of 24 hr. Blood samples for F concentrations were obtained prior to placement of the TTS and at 4, 8, 12, and 24 hr after TTS placement, and at 6, 12, and 24 hr after TTS removal. Standardized anesthesia was as follows: F 200 ug IV, thiopental 4 mg/kg IV, atracurium 0.4 mg/kg IV, succinylcholine IV as necessary. Gas mixture was 66% N_2O, 33% O_2, and 0 to 1.5% isoflurane as necessary. In the event of inadequate analgesia, standardized supplemental morphine injections were provided.

After return to the surgical wards, the pts were monitored using a pulse oxymeter, apnea alarm, and continuous nursing observation for a period totalling 36 hr after TTS placement. Blood pressure (BP) was measured every 4 hr and other vital signs hourly. Pts rated their pain, nausea and sedation hourly while awake, using a 10 point digitized analog scale. Observers rated sedation hourly on a 5 point scale. Global assessments were performed at 24, 36, and 48 hr by both the pts and nurse observers. Data were analyzed for 5 postoperative time periods: Recovery, Ward-12 hr, 12-24 hr, 24-30 hr, and 30-36 hr. Examination of the skin site occluded by the TTS was performed at 1, 6, and 24 hr after TTS removal. The TTS was removed early under the following circumstances: Recovery room - pCO_2 > 55mmHg; Ward - respirations < 8/min, hemoglobin O_2 saturation < 90% while breathing supplemental O_2, maximal observer sedation rating for 6 consecutive hr, inadequate analgesia after 3 consecutive morphine supplements, systolic BP < 70 mmHg, heart rate < 50 beats/min. Naloxone was given if necessary.

Statistical analyses of demographic data were made using the t test, Fisher's exact test, and Chi-square statistic, as appropriate. Comparison of morphine use and analog scale ratings between groups was made using the Wilcoxon 2-sample rank sum test.

Results: 43 pts were enrolled in the trial (22 F, 21 placebo (P)). 37 were evaluable for efficacy and side effects. 6 pts had the TTS removed pre- or intraoperatively (3 from each group). The P and F groups were not significantly different with respect to age, sex, race, height, weight, ASA class, surgical procedure, or number of previous surgeries. F pts used supplemental morphine at a lower rate than did P pts throughout the study, though this difference did not reach statistical significance at the 0.05 level. The most significant difference (p=0.058) occurred during the 12-24 hr study period, when P pts used morphine at a rate twice that of F pts (mean rates 1.0 mg/hr and 0.5 mg/hr, respectively). Pain intensity scores were not significantly different between groups except during the 30-36 hr study period, when the F group had higher pain scores (F:5.7; P:3.9, on scale of 0-9). Global pain control scores were similar between groups. F concentrations at 8, 24, and 36 hr were (mean (S.D.)): 1.16 (0.87), 1.52 (0.85), 1.01 (0.59) ng/ml.

Vital signs remained stable in all pts throughout the study with the following exceptions: 2 pts in the F group failed to breathe spontaneously immediately after extubation. Both responded rapidly to naloxone. One additional pt in each group developed ventilatory depression on the ward. This resolved without intervention in the F pt. Nausea and vomiting was the most prominent adverse experience in both groups, occurring in 36% of the F and 24% of the P pts while on the ward with the TTS in place. Pts in both groups generally rated their nausea as mild (1-2 on a scale of 0-9). Sedation was mild to moderate in both groups. Mean sedation scores were not significantly different during any study period. The incidence of skin irritation was low. Mild erythema was noted in 7 pts in each group. Itching was reported by 4 F pts, and papules were observed in 1 F pt. All dermatologic effects resolved by 24 hr after TTS removal.

Discussion: Transdermal F (TTS (fentanyl)) in doses of 75 ug/hr was well tolerated in the majority of pts. The concept of a transdermal system for postoperative pain control was very well received by the majority of pts. In this group of orthopedic and abdominal surgery pts, the dosage administered provided a component of pain relief as evidenced by lower supplemental morphine usage in the F group. A higher F administration rate may be required for optimal analgesia in pts undergoing similar surgical procedures.

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