Exhibit 1012

The Relative Potency of Oral Transmucosal Fentanyl Citrate Compared with Intravenous Morphine in the Treatment of Moderate to Severe Postoperative Pain

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Pharmacokinetic studies have shown that oral transmucosal absorption of fentanyl is relatively rapid compared with gastrointestinal absorption, and it results in increased bioavailability. We designed this study to establish the relative potency of oral transmucosal fentanyl citrate (OTFC) compared with IV morphine in 133 postoperative patients. The morning after surgery, patients randomly received one dose of either OTFC (200 or 800 μg) and a placebo IV injection or IV morphine (2 or 10 mg) and an oral transmucosal placebo unit. Pain intensity, pain relief, time to meaningful pain relief, and time to remedication were recorded. Median time to onset of relief was approximately 5 min for all groups. Over the first hour, little difference among treatment groups was seen for pain intensity and pain relief. By 2 h after study drug administration, 800 μg of OTFC and 10 mg of IV morphine generally produced similar analgesia, which was better than the smaller doses. Duration of analgesia with the larger doses (800 μg of OTFC and 10 mg of morphine) was similar and longer that produced by the smaller doses. The larger doses of OTFC and morphine produced better and more sustained analgesia than 200 μg of OTFC or 2 mg of morphine. **Implications:** The relative potency of oral transmucosal fentanyl citrate (OTFC) to IV morphine was 8–14:1. In this postoperative setting, OTFC produced rapid pain relief similar to that produced by IV morphine. The larger doses of OTFC (800 μg) and morphine (10 mg) produced better and more sustained analgesia than 200 μg of OTFC or 2 mg of morphine.

(Anesth Analg 1999;89:732–8)

Oral transmucosal fentanyl citrate (OTFC) is a noninvasive delivery system for fentanyl (1). The OTFC unit consists of a sweetened matrix containing fentanyl that is attached to a handle. When OTFC is placed in the mouth and sucked by the patient, the matrix dissolves and fentanyl is absorbed through the oral mucosa to provide fast-acting analgesia.

OTFC is currently being studied as a treatment for breakthrough pain in patients with cancer (2). Breakthrough pain is a flare of severe pain that exceeds the analgesia from the long-acting medication that is administered at regular intervals to manage a patient's persistent pain. OTFC is intended to be used in conjunction with a long-acting opioid to manage these flares of intense, often excruciating, pain. The utility of OTFC for managing postoperative pain is also being evaluated.

It is important to understand the relative potency of new analgesics given via a new route of administration. Therefore, the present study was designed to determine the relative potency of OTFC to IV morphine in postoperative patients. This population is ideal for studying analgesics because of the ability to find a relatively standardized pain model. The relative potency of new analgesics is often compared with morphine, because morphine is the standard of care in the treatment of pain. Ashburn et al. (3) evaluated

This work was supported by a grant from Anesta Corp., Salt Lake City, UT.

Presented in part at the 1996 APS meeting, Washington, DC; at the 1997 Congress of the European Federation of IASP Chapters, Barcelona, Spain; and at the 1997 annual meeting of the IARS, San Francisco, CA.

Accepted for publication April 22, 1999.

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0003-2999/99

multiple administrations of OTFC in patients recovering from total hip replacement or knee arthroplasty in a morphine patient-controlled analgesia (PCA)-sparing model and estimated that 1 mg of OTFC seemed to be as potent as 5 mg of IV morphine. Their study, however, did not formally evaluate the relative potency of OTFC. In the present randomized, double-blinded, parallel-group, four-point study, we evaluated the relative potency of OTFC and IV morphine after single-dose administrations.

Methods

After institutional approval, written informed consent was obtained from patients 18–79 yr (ASA physical status I or II) scheduled for lower abdominal surgery in which PCA was planned for postoperative pain control. Excluded were patients with clinically significant laboratory abnormalities, patients taking medications that could confound the quantification of or need for analgesia, patients with a history of drug or alcohol abuse, and pregnant and lactating women.

This randomized, double-blinded, four-point, parallel-group study took place at five different hospitals. Patients were randomly assigned to one of four active treatments: 200 μg of OTFC, 800 μg of OTFC, 2 mg of IV morphine, or 10 mg of IV morphine. The 800-μg OTFC dose was selected because it had repeatedly proved effective and safe. A pilot study comparing 200 and 400 μg of OTFC was conducted to determine which of those doses should be used as the small OTFC dose in the four-point study. The 200-μg dose was found to be the minimal effective dose and therefore was used. Similarly, the doses of IV morphine used in the four-point study were determined in a separate pilot study. Doses of 2 and 10 mg of IV morphine were selected based on the results of this pilot study. Patients were assigned a sequential number in the order they entered the study. Before the study, sequential numbers were randomly assigned to one of the four treatment groups, with randomization stratified in blocks of four so that exactly one sequence number in each block was assigned to each treatment group. Because of the different routes of administration, a double-dummy blinding technique was used. Patients receiving OTFC also received a placebo IV injection; patients receiving IV morphine also received an oral transmucosal (OT) placebo. The packaging and appearance of the active and placebo OT units were indistinguishable, and the packaging for active and placebo IV injection was indistinguishable. Both the patient and investigator were blinded to study medication given to the patient. Patients were instructed to suck on the OT unit actively and to consume it completely within 15 min.

Surgery and anesthesia were performed according to customary practice at each institution. Intraoperative medications were not restricted because the study would commence the day after surgery. Patients were allowed to recover for the remainder of the surgical day and the first night (minimum of 8 h before study start). After surgery and up until study start, patients had access to PCA morphine for pain control. At approximately 6:00 AM after surgery, PCA was discontinued. Patients who did not experience moderate to severe pain within 4 h after discontinuation of PCA did not qualify for the study. PCA morphine use from midnight through PCA termination was recorded. Patients with nasogastric tubes had their nasogastric tube clamped immediately before study initiation.

At the patient's first request for analgesia for moderate to severe pain, the study medications were administered. Patients were given a stopwatch, which was started with the administration of study medications, and they were asked to stop the watch when meaningful pain relief occurred. Study drug evaluations were made using 100-mm visual analog scales (VAS) that measured pain intensity (0 = no pain to 100 = worst pain imaginable) and pain relief (0 = no pain relief to 100 = complete pain relief). Pain intensity was measured immediately before study drug administration (time 0); 15, 30, 45, and 60 min after start of study drug administration; and hourly for the next 5 h (total of 6 h). Pain relief was measured 15, 30, 45, and 60 min after start of study drug administration and hourly for the next 5 h. Final pain intensity and pain relief scores were obtained on study termination. No attempts were made to obtain pain by evoked stimuli. At the end of the study, patients globally assessed drug efficacy using a 5-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent). Duration of the study was a maximum of 6 h, or the time from the dose of test medication until patients requested additional analgesia. Patients were encouraged to remain in the study for at least 1 h.

A study nurse remained with the patients throughout the study. Pulse oximetry was monitored continuously, and vital signs (respiratory rate, heart rate, and blood pressure) were recorded at the same time as the VAS pain scores. Adverse events were recorded.

Several measures of analgesia were derived from the data. Because pain intensity as measured by VAS varied among patients at study start, pain intensity difference (PID) was calculated. PID is the difference between pain intensity scores at baseline and at an observation point. The area under the PID curve was summed and weighted by the time interval between measurements to determine the summed pain intensity difference (SPID). The area under the pain relief curve, weighted for time, was also determined (TOTPAR). Scores were weighted to correct for differences in time intervals between assessments (pain

measurements were taken every 15 min for the first hour and then hourly for the remaining 5 h). SPID was also normalized for each patient to express these scores as a percentage of the maximal possible score for each patient. Normalization helps to ensure that patients with higher pain intensity scores at baseline are not overrepresented compared with patients with lower baseline scores. For patients terminating the study before 6 h, the last observation was carried forward for pain intensity and pain relief scores.

Two-way analysis of variance (treatment group, center, and treatment group by center) was used to compare the four treatment groups with respect to age, weight, baseline pain intensity scores, SPID, and TOTPAR at every time point. A Wilcoxon survival analysis was used to compare treatment groups for time in the study and time to meaningful relief. Sex and global assessment of pain relief were evaluated using a Cochran-Mantel-Haenszel test stratified by centers (4). The exact permutation test was used for the proportion of patients who remained in study at least 1 h. A two-sided $P < 0.05$ was considered statistically significant. The relative potency of OTFC to morphine was assessed by using a general linear model, regressing the dependent variable (SPID and TOTPAR) on log-transformed dose level, and it included a test for parallelism of the two dose-response curves (5).

Results

All 133 patients were included in safety analyses, but 10 were excluded from efficacy analyses because of protocol violations. Five patients received a concomitant medication before study start that could have confounded the quantification of analgesia, two patients did not consume at least 90% of the study drug, and three patients were enrolled at a site that did not have at least one evaluable patient in every treatment group. There were no significant differences among treatment groups for any demographic variable (Table 1). Mean consumption times of the OT unit across the groups was 14–17 min (individual times were 6–31 min). Data from patients with consumption times >20 min ($n = 10$) were excluded from some efficacy evaluations (time until meaningful relief, proportion of patients experiencing meaningful relief, global assessment, and pain intensity and pain relief scores before 60 min). Except for cumulative PCA use from 4 AM to PCA discontinuation, there were no statistically significant treatment group differences (Table 2).

There was no statistical difference in SPID scores among groups up to 60 min after study drug administration, although, at 60 min, the difference between the two morphine groups approached significance ($P = 0.07$) (Fig. 1). At 120 min postdose and later, the average SPID scores in the 800 μg of OTFC and 10 mg of IV morphine (large dose) groups were statistically different from the average of the 200 μg of OTFC and 2 mg of IV morphine (small dose) groups ($P \leq 0.04$ at each time point).

In the first hour, 800 μg of OTFC produced less total pain relief (TOTPAR) than 200 μg of OTFC or 10 mg of IV morphine ($P \leq 0.051$ at each time point), whereas 10 mg of morphine provided more pain relief than 2 mg of morphine ($P \leq 0.02$ at each time point) (Fig. 2). By 2 h, TOTPAR scores for the large doses and small doses began to separate, with statistically significant differences between the large- and small-dose groups 4, 5, and 6 h postadministration ($P \leq 0.03$).

All four test medications had a rapid onset of action, and there was no significant difference among groups in time to onset of relief. Median time for onset of pain relief for either dose of OTFC was 4.2 min (range 0.4–32.3 min). Median time to relief was 5.4 min (0.2–13.7 min) for 2 mg of morphine and 3.8 min for 10 mg of morphine (0.2–34.3 min).

The large-dose treatments produced the longest analgesia and were very similar. Patients who received 800 μg of OTFC remained in the study for a median of 215 min, and patients who received 10 mg of morphine remained in the study for a median of 188 min ($P = 0.69$). Median times that patients receiving 200 μg of OTFC or 2 mg of morphine remained in the study were 145 and 130 min, respectively. Patients receiving 800 μg of OTFC or 10 mg of morphine had a significantly longer time to remedication than patients receiving either of the smaller doses ($P \leq 0.04$). Six patients remained in the study <1 h. Of these patients, one had received 200 μg of OTFC, two had received 800 μg of OTFC, and three had received 2 mg of morphine. The proportion of patients remaining in the study at least 1 h did not differ among treatment groups ($P = 0.27$).

Patients provided a global assessment of their pain relief. Of patients receiving 200 or 800 μg of OTFC, 77% or 74%, respectively, rated their pain relief as either very good or excellent, compared with 43% of patients receiving 2 mg of morphine and 64% of patients receiving 10 mg of morphine. The median assessment by patients who received either dose of OTFC or 10 mg of IV morphine was 2 (very good). The median score by patients receiving 2 mg of morphine was 3 (good). There was no significant difference among treatment groups (Table 3).

Relative potency estimates of OTFC to IV morphine are shown in Figure 3. Relative potency estimates were performed only when the test for parallelism was not statistically significant ($P > 0.05$) and only when the common slope was statistically significant ($P < 0.05$). Thus, relative potency was not calculated for pain relief before 3 h. Relative potency estimates

Table 1. Patient Characteristics

	Oral transmucosal fentanyl citrate		Morphine	
	200 μg (n = 33)	800 μg (n = 32)	2 mg (n = 34)	10 mg (n = 34)
Sex (male/female)	3:30	1:31	1:33	1:33
Age (yr)	42 ± 10	41 ± 8	43 ± 10	47 ± 9
Weight (kg)	71 ± 15	71 ± 13	71 ± 17	73 ± 13
Surgical procedure[a]				
Hysterectomy (noncancer)	16	19	18	18
Hysterectomy (cancer)	5	4	7	9
Other gynecological	9	8	7	5
Colorectal	2	1	1	1
Other	2	1	1	2

Values are mean ± SD or n.
n = 133.
[a] Some patients underwent more than one surgical procedure.

Table 2. Baseline Comparisons[a]

	Oral transmucosal fentanyl citrate		Morphine	
	200 μg (n = 30)	800 μg (n = 30)	2 mg (n = 31)	10 mg (n = 32)
Cumulative PCA morphine use (mg)	10.1 ± 7.4	7.4 ± 4.4*	10.5 ± 6.8	8.9 ± 5.1
Total PCA morphine use (mg)	17.7 ± 10.6	15.8 ± 10.5	18.1 ± 10.4	17.0 ± 9.7
Minutes from PCA off to baseline	47 ± 37	39 ± 35	40 ± 32	57 ± 52
Pain intensity score				
PCA off	30 ± 20	38 ± 24	36 ± 22	30 ± 21
Baseline	51 ± 24	54 ± 22	49 ± 22	49 ± 20

Values are mean ± SD.
* P = 0.02 versus 200 μg of oral transmucosal fentanyl citrate and 2 mg of morphine.
[a] The data of 10 patients were considered unevaluable due to protocol violations and are not included.

ranged from 10 to 14 for SPID scores and from 7.5 to 7.9 for TOTPAR total pain relief scores. Time in study to remedication produced a relative potency estimate of 14.

Oxygen desaturation clinically diagnosed as hypoventilation occurred in one patient who received 200 μg of OTFC and in one patient who received 10 mg of morphine (Table 4). Both patients received supplemental oxygen. No patients had a serious drug-related adverse event. No patients terminated the study early because of adverse events.

Discussion

The primary purpose of this study was to determine the relative potency of OTFC to IV morphine. SPID scores were statistically higher for the large-dose groups than for the small-dose groups beginning at two hours. However, for pain relief, the difference was not statistically significant until four hours. Based on pain intensity scores beginning at two hours, pain relief scores beginning at three hours, and time until requested additional analgesia, the relative potency of OTFC to IV morphine was calculated to be 8–14:1.

The lack of difference before two hours between the large- and small-dose groups is likely due to study design. All patients had adequate analgesia with IV PCA before the study period and theoretically should have required only small doses of opioid to maintain plasma opioid levels in the analgesic range. Effective use of PCA results in the plasma level of the analgesic, morphine, being kept close to the minimal effective analgesic concentration. Austin et al. (6) demonstrated that only a small change in the plasma level of an opioid was associated with the transition from pain to analgesia. Because only a small change in plasma concentration was required to produce analgesia in these patients, this analgesic threshold was exceeded by even the smaller doses of morphine and OTFC. The larger doses of morphine and OTFC theoretically exceeded this threshold and maintained the blood level above the threshold for a longer period. Although the pain relief scores of patients who received 200 μg of OTFC were significantly better than those of patients who received 800 μg of OTFC during the first hour, it is doubtful that this difference is clinically relevant. The residual amount of morphine that was undoubtedly present before either OTFC or IV

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