Pharmacology of Epidural Fentanyl, Alfentanil, and Sufentanil in Volunteers

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Background: Despite a large number of clinical investigations in postoperative patients, the pharmacology of epidural fentanyl, alfentanil, and sufentanil has not been well characterized in a human laboratory setting. In this double-blind, placebo-controlled crossover study, we evaluated analgesia and side effects produced by epidural fentanyl (30 and 100 μg), alfentanil (300 and 1,000 μg), and sufentanil (3 and 10 μg) in volunteers.

Methods: Each of 12 volunteers participated in four separate study sessions. The pain model was cutaneous electrical stimulation of intensity sufficient to produce a pain report of 5 on a 0–5 scale, delivered alternately to the finger and toe. Ventilatory drive, pupil size, and subjective ratings of alertness, nausea, and pruritus were measured using visual analog scales. On each study day, after baseline measurements, an epidural catheter was placed at the L2–L3 or L3–L4 interspace. Subjects received the small dose of study drug, and the tests were repeated at 2, 5, 5, and 95 min after drug administration. Subjects then received the large dose of the same study drug, and the series of tests was repeated at 2, 5, 5, and 95 min later. Plasma opioid concentrations were measured using gas chromatography-mass spectrometry.

Results: Dose-dependent analgesia was found for all study opioids. For both doses of all opioids, toe analgesia was significantly greater than finger analgesia. Epidural fentanyl and alfentanil provided greater analgesia than sufentanil at the doses investigated. Sedation, increased end-tidal carbon dioxide, and pupillary constriction occurred only after the large epidural doses of all opioids. Overall, the incidence of subjective side effects was low, but four subjects experienced pruritus after 100 μg fentanyl, and four were nauseated after 1,000 μg alfentanil. Plasma opioid concentrations were near minimum effective analgesic plasma concentrations only after larger epidural doses.

Conclusions: Lumbar epidural fentanyl, alfentanil, and sufentanil produce selective lower-extremity analgesia. Low plasma opioid concentrations measured after small epidural opioid doses suggest a spinal mechanism for analgesia. Larger doses of epidural opioids result in systemic absorption and are likely to produce supraspinal analgesia and other side effects. (Key words: Analgesics, opioid: alfentanil; fentanyl; sufentanil. Anesthetic techniques: epidural.)

ONLY a few years after a spinal site of action for opioids was discovered, clinical investigators described intrathecal and epidural morphine administration for treatment of severe pain in humans.1,2 After these early reports, Bromage, Camporesi, and colleagues3–5 described analgesia and respiratory and nonrespiratory effects of epidural morphine in normal volunteers. They reported cephalad progression of analgesia and cutaneous hypalgesia over time, as well as delayed and prolonged side effects, including respiratory depression, pruritus, nausea, and vomiting, and urinary retention. These observations reflect extensive cephalal spread of morphine in cerebrospinal fluid (CSF) and correlate well with the later findings of Gourlay et al.,6 who reported peak cervical CSF morphine concentration 3 h after lumbar epidural administration. Cousins and Mather,7 in a comprehensive review of intrathecal and epidural opioids, suggested that lipophilic opioids may offer a better efficacy-safety ratio than morphine. In theory, lipophilic drugs would be less likely to persist in CSF and thus less likely to cause undesirable brain effects including respiratory depression. Much literature has accumulated in recent years describing the efficacy and safety of epidural fentanyl and its derivatives for management of acute pain states. However,
little information has been published regarding analgesia and side effects of epidurally administered lipophilic opioids in controlled human laboratory studies.

We compared the pharmacology of the lipophilic opioids fentanyl, sufentanil, and alfentanil in a manner similar to that of Bromage and colleagues, to gain information about the epidural use of these drugs in a controlled setting that would complement the extensive clinical experience. We hypothesized that epidural fentanyl, alfentanil, and sufentanil would provide selective analgesia of the lower extremity and produce few or no supraspinal side effects. In this double-blind, placebo-controlled crossover laboratory investigation, we measured the time course and spread of analgesia, the magnitude and time course of respiratory and non-respiratory side effects, and plasma opioid concentrations after epidural administration of fentanyl, alfentanil, sufentanil, and saline in normal volunteers.

Methods

All subjects participated in four study sessions, each separated by at least 10 days. On each study day, subjects were given two doses of one of the four study drugs, fentanyl, sufentanil, alfentanil, or placebo (saline). In this crossover study, each subject received all four study drugs, given in a double-blind, randomized sequence.

Subjects

Twelve healthy volunteers, eight men and four women, aged 22–28 yr (mean 24.7 yr) were recruited for this study. Body weight range was 48.4–84.2 kg (mean 67.5); all subjects were within ±10% of normal weight for height. One female subject was taking oral birth control pills, and one male was using topical minoxidil; no other subjects were using medications of any kind, and none reported any history of drug or alcohol abuse. All subjects gave written informed consent as approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Experimental Pain Model

The pain model used in this study was cutaneous electrical stimulation of intensity sufficient to elicit pain under normal circumstances, delivered alternately to the finger of the nondominant hand and an ipsilateral toe. For stimulus delivery, a 1 mm² area of skin was abraded with a dental burr, and a silver electrode was taped in place. At the start of each study session, we increased the stimulus intensity gradually until the subject reported "strong pain" on a six-point scale (0 = faint sensation, 1 = very faint pain, 2 = faint pain, 3 = mild pain, 4 = moderate pain, 5 = strong pain). Stimulus intensities required to elicit a rating of 5 were determined separately for the toe and the finger. We established that these intensities elicited a consistent rating of 5, corresponding to strong pain, by requiring baseline ratings to average greater than 4.8. These same stimulus intensities were then used for the subject throughout that study day. Stimulus intensities were established anew on each study day; but for each individual subject, stimulus intensities for finger and toe remained similar across all test days. Analgesic effect was assessed by subjects' rating using the aforementioned six-point scale (i.e., pain report).

A Grass Model 44 stimulator (Quincy, MA) with constant current and stimulus isolation units produced repeating 5-ms square wave pulses of 0.5–2-mAmp intensities. The interstimulus interval varied between 4 and 6 s (average 5 s). We maintained skin impedance within the range of 2–10 KΩ at the stimulus intensity required to elicit a pain report of 5 to ensure constant stimuli. Painful stimuli were delivered alternately to the toe, then to the finger, in sets of 50 stimuli (25 each site). Subjects rated the intensity of each stimulus by moving the pointer of a slide potentiometer along a 5-cm scale marked to correspond to the pain scale described above. Individual pain reports were averaged separately for the toe and finger at the end of each 50-trial set (25 stimuli/site). Each stimulation set required approximately 4 min for completion. To characterize the time course of analgesia, we delivered stimuli at 2, 7, 12, 55, 60, 65, 98, 103, and 108 min after each epidural dose.

We quantified analgesia as a decrease in subjective pain report. In addition to ratings of pain intensity at each time point, we calculated time-averaged mean pain reports for the 2-h period after each epidural dose. These values were determined by calculating the area under the pain report versus time curves and dividing by 120 min (duration of analgesia testing after each dose.)

Cutaneous Sensory Change and Motor Strength

We determined sensitivity to pinprick and to ice on the skin of the abdomen, thighs, and legs. Subjects were asked to rate sharp and cold sensation compared to a reference point on the upper arm. Sensation was graded.
simply as the same or less sharp or cold compared to the reference point. Motor strength was measured using a five-point scale as follows: 0 = unable to move, 1 = trace movement, 2 = movement with gravity eliminated, 3 = movement against gravity but not resistance, 5 = normal strength.

**Ventilatory Effects**
We measured end-tidal carbon dioxide (ETCO2), minute ventilation (Ve), and carbon dioxide production (VCO2) while the subject was at rest and breathing through a standard spirometry mouthpiece and tubing. We used an Andros OEM model 412 carbon dioxide analyzer (Andros, Berkeley, CA) for detection of ETCO2 and a Pneumotach model 3183 (Hans Rudolph, Kansas City, MO) to calculate breath-by-breath minute ventilation. We also measured ventilatory response to increasing inspired carbon dioxide concentration, using the rebreathing method of Read9 and calculated the slope and x-intercept of the regression of Ve on ETCO2 partial pressure during rebreathing. We have used this methodology in previous laboratory studies comparing intravenous infusions of morphine, fentanyl, alfentanil, and sufentanil, as well as interactions between alfentanil and propofol in volunteers.10-12 A respiratory depressant can shift the ventilatory response curve to the right without changing the slope, change the slope of the ventilatory response curve without shifting it, or both. Therefore, from the regression of minute ventilation on ETCO2 curve, we also calculated the Ve55, i.e., the minute ventilation at an ETCO2 of 55 mmHg. This calculation includes both changes in slope and rightward shift of the ventilatory response curve and thus may be a more sensitive measurement of ventilatory depression than slope or x-intercept alone.

**Pupilometry**
We measured pupil size using a modified Essilor pupilometer as described by Ravnberg et al.13 After allowing 30 s for light adaptation, we recorded the maximum pupil diameter measured during a 10-s observation period.

**Subjective Side Effects**
Subjects rated intensities of side effects using 100-mm visual analog scales (VAS) for nausea, pruritus, alertness, and mood. Nausea and pruritus scales were anchored by “none” and “worst possible,” the alertness scale was anchored by “can’t keep my eyes open” and “wide awake,” and the mood scale was anchored by “best I’ve ever felt” and “worst I’ve ever felt.”

**Drug Administration**
On each study day, the subject received in succession a small and large dose of the study opioid or equal volume of saline (placebo). The doses used were 30 and 100 µg fentanyl, 300 and 1,000 µg alfentanil, and 3 and 10 µg sufentanil. All doses were administered in a 6-ml volume over 3–5 min. These doses are half-log increments and were chosen based on intravenous dose equivalence for analgesia.

**Test Sessions**
Subjects fasted after midnight before each study day. A urine pregnancy test (HCG-Urine CARDS, Pacific Bio-tech, San Diego, CA) was performed on the morning of each study session for all female volunteers. Each session took place in a sound-attenuated chamber with the subject seated in a hospital bed. At the beginning of each study day, a 20-G catheter was placed in an antecubital vein of one arm for fluid administration and an 18-G catheter in a vein of the opposite arm for serial blood sampling. Baseline measurements were collected for pain report (pain report), sensory and motor function, subjective side effects, ventilatory function, and pupil size. After baseline measurements, the subjects assumed a left lateral decubitus position, and an epidural catheter was placed at the L2–L3 or L3–L4 interspace via an 18-G Tuohy-Schiff needle with a midline approach and advanced 2.5–3 cm into the epidural space. A test dose of 10 µg epinephrine in 2 ml saline was used to rule out intravascular placement. At the end of each study day, epidural catheter placement was confirmed using 7–10 ml 1% lidocaine to obtain a dermatomal distribution of sensory blockade. Confirmation with local anesthetic was done at the end of the day to avoid potential interaction between local anesthetic, even at subclinical doses, with the study opioid.

One hour after the epinephrine test dose, the subject received the small dose of study drug. The series of tests, including three sets of pain intensity ratings, sensory and motor function, pupil size, and subjective side effect ratings, was administered at 2, 55, and 98 min after drug administration. Ventilatory drive was measured 30 min after drug administration. Exactly 2 h after the small-dose administration, the large dose of the same study drug was administered, and the test battery was repeated at the same times as after the low dose. A final series of tests, including ventilatory drive,
was performed at 3 h after the large dose was administered (i.e., washout period) to determine whether drug effects had returned to baseline values. Serial blood samples (10 ml) were collected at frequent intervals after each epidural drug dose and kept on ice until the end of the study day. Blood samples were centrifuged, and the plasma was frozen for analysis on a later date.

Plasma Opioid Concentration

Plasma fentanyl, sufentanil, and alfentanil concentrations were determined by gas chromatography-mass spectrometry. The method of Woestenborghs'14,15 was modified to increase sensitivity. This method consists of a multistep liquid-liquid extraction of plasma, concentration of the extract, and gas chromatography-mass spectrometry analysis of the extracts. Various amounts of plasma were extracted, depending on the expected concentrations, for the determination of all three drugs. An internal standard was used to correct for drug recovery throughout the extraction and analytical process. Selected ion monitoring was used to increase sensitivity.

Analysis of sufentanil required us to extract a large amount of plasma (5 ml) to increase the quantity of sufentanil in the sample extract. Our analytical limit of detection was 2 pg injected into the column. This is equivalent to a detection limit of 0.002 ng/ml. This extreme limit of detection was necessary for the determination of the concentrations of sufentanil after the smaller epidural dose. We were required to make several modifications to our standard sufentanil assay to achieve these levels. In addition to extracting large plasma samples, we could analyze samples only after a rigorous cleaning of the mass spectrometer source and injector. We also injected one-fifth of our sample extract using an increased injector pressure technique to more fully transfer sample into the column. The interday coefficient of variation was 11.5% at 0.02 ng/ml. The coefficient of variation at 0.002 ng/ml was approximately 30%.

For alfentanil analysis, we extracted a 1-ml plasma sample using our standard method. The detection limit was 0.05 ng/ml with an interday coefficient of variation of 7.56% at 19.87 ng/ml. Fentanyl analysis required a 3-ml plasma sample, again to increase our sensitivity. Instrument preparations similar to the setup for sufentanil were used. The limit of detection was 0.025 ng/ml with an interday coefficient of variation of 6.60% at 0.25 ng/ml.

Data Analysis

We first examined effect variables by graphing each measurement, e.g., pain report, pupil size, and EtCO₂ versus time, and then analyzed them statistically using repeated measures analysis of variance (ANOVA). The analysis of analgesic effect tested drug, dose, and site (finger versus toe) effects, as well as drug × dose, drug × site, and drug × site × dose interactions overall including the saline condition and across all three opioids excluding saline. A significant drug main effect indicates that the average effects of drugs differed but not whether the difference is influenced by the dose or site of stimulus. For analgesia, a site main effect indicates only that average analgesia was different at the finger and toe but not whether this difference depends on the drug or dose. Similarly, a dose main effect shows that the responses differed with small or large doses but not whether the dose effect was different at the two stimulus sites or with different drugs. A drug × dose interaction means that the difference in drug effect depends on dose, and a drug × site interaction means that the difference in drug effect depends on stimulus site. A drug × site × dose interaction would indicate a complex interaction among these three variables. When interactions are present, main effects usually are not interpretable. Significant differences were followed by paired comparisons using ANOVA and post hoc paired t tests where indicated. Side effects were analyzed in one of two ways. Respiratory effects (viz. EtCO₂ and V₅₅₅ calculated from the hypercapnic ventilatory response curve), pupil size, and VAS for alertness were examined for drug, dose, and drug × dose effects using ANOVA. VAS ratings for nausea and pruritus showed very skewed distributions that could not be treated as even approximately normal. Therefore, we defined presence or absence of nausea and pruritus as a VAS score of 20 mm or greater and examined differences in frequencies using Cochran’s Q test. We also tested whether the presence of a side effect with one drug predicted its occurrence with another drug using Kendall’s coefficient of concordance. Differences were considered significant at P < 0.05. For variables analyzed by ANOVA, normal theory standard errors are reported with the mean values.

Results

Demographics and Complications

Twelve healthy volunteers, eight men and four women, aged 22–28 yr (mean 24.7 yr) participated in
Fig. 1. Pain report for finger (open circles) and toe (filled circles) after epidural fentanyl (A), alfentanil (B), sufentanil (C), and placebo (D). Arrows indicate the times of administration of small and large epidural doses. Pain report at each time point is the average of 25 trials at each site. Values are mean ± SEM for 12 subjects.

this study. Body weight range was 48.4–84.2 kg (mean 67.5); all subjects were within ±10% of normal weight for height. One female subject was taking oral birth control pills, and one male was using topical minoxidil; no other subjects were using medications of any kind, and none reported any history of drug or alcohol abuse. All subjects refrained from caffeine, alcohol, and all analgesic use for at least 24 h before each study day.

Ten subjects reported brief, mild paresthesias on insertion of the epidural catheter on each study day, but no paresthesias persisted, and none required additional attempts at epidural catheter placement. Nine subjects reported vague abdominal, back, or hip pressure with injection of all epidural study drugs (including placebo), but none reported any sensation with injection of local anesthetic at the end of the study day. All female subjects who reported sensations with epidural drug injection stated that the feeling was similar to a menstrual cramp.

Analgesia

Analgesia was quantified as a reduction in pain report, a subjective rating of pain intensity to electrical stimulation of the finger and toe. Mean finger and toe pain reports measured over the entire course of study with each epidural opioid and placebo are shown graphically in figure 1. The onset of analgesia (decrease in pain report) occurred within 15 min for small doses and 10 min for large doses of all epidural opioids. Pain report decreased in a dose-dependent fashion for fentanyl (fig. 1A), alfentanil (fig. 1B), and sufentanil (fig. 1C) but only minimally for placebo (fig. 1D). The time course and magnitude of analgesia were nearly identical for epidural fentanyl and alfentanil, but at doses used in this study, epidural sufentanil produced significantly less analgesia than fentanyl and alfentanil (P values in table 1). After the small doses, mean peak analgesia was achieved near 60 min; after large doses, maximum
Table 1. Multivariate Analysis of Analgesia Assessment and Post Hoc Paired t Tests

<table>
<thead>
<tr>
<th>Effect</th>
<th>Repeated measures ANOVA</th>
<th></th>
<th>Study Opioids Only</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>F</td>
<td>P</td>
<td>df</td>
</tr>
<tr>
<td>Drug</td>
<td>3,9</td>
<td>10.17</td>
<td>0.003</td>
<td>2,10</td>
</tr>
<tr>
<td>Site</td>
<td>1,11</td>
<td>11.51</td>
<td>0.006</td>
<td>1,11</td>
</tr>
<tr>
<td>Dose</td>
<td>1,11</td>
<td>29.36</td>
<td>&lt;0.001</td>
<td>1,11</td>
</tr>
<tr>
<td>Drug × site</td>
<td>3,33</td>
<td>4.44</td>
<td>0.010</td>
<td>2,11</td>
</tr>
<tr>
<td>Drug × dose</td>
<td>3,9</td>
<td>9.52</td>
<td>0.004</td>
<td>2,10</td>
</tr>
<tr>
<td>Site × dose</td>
<td>11,1</td>
<td>0.35</td>
<td>0.568</td>
<td>1,11</td>
</tr>
<tr>
<td>Drug × site × dose</td>
<td>3,9</td>
<td>2.30</td>
<td>0.145</td>
<td>2,10</td>
</tr>
</tbody>
</table>

Paired t Tests (P values)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Sufentanil</th>
<th>Alfentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toe analgesia versus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>&lt;0.001</td>
<td>0.029</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>&lt;0.001</td>
<td>0.044</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.022</td>
<td>—</td>
</tr>
<tr>
<td>Finger analgesia versus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.001</td>
<td>0.036</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.003</td>
<td>0.062</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.064</td>
<td>—</td>
</tr>
</tbody>
</table>

Significance was assessed by exact multivariate F tests, which are always valid, or more powerful univariate (averaged) F tests, as warranted.

analgesia (lowest pain report) occurred at 15 min. Although there was large individual variation, the duration of effect was approximately 2 h for both small and large doses of all three opioids. Table 1 summarizes the results of the ANOVA on analgesic effects across all treatments and across opioids only as well as P values for follow-up paired t tests performed when significant differences were identified by ANOVA. We found significant differences between drugs, between sites of stimulation, and between doses (either including placebo or not including placebo). The differences between drugs depended on the dose as revealed by a significant interaction term (i.e., drug × dose) but did not depend on sites of stimulation. None of the other interaction terms reached statistical significance. Therefore, the differences between stimulation sites did not depend on the drug or the dose of the drug. Likewise, the differences between doses did not depend on the drug or the stimulation site.

We found that analgesia was relatively selective for the lower extremity. Toe analgesia was consistently greater than finger analgesia in all cases. Significant differences between the overall ratings of toe and finger analgesia were confirmed with post hoc paired t tests for fentanyl ($P < 0.05$), alfentanil ($P < 0.01$), and sufentanil ($P < 0.05$).

Time-averaged mean pain reports for the 2-h period after each epidural dose and their significance compared to baseline values are shown in Table 2. Time-averaged pain reports were significantly lower than mean baseline pain reports for both doses of all study drugs, but the magnitude of decrement in pain report

Table 2. Mean Pain Report Averaged over Each 2-Hour Period after Epidural Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Small Dose</th>
<th></th>
<th>Large Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Toe</td>
<td>Finger</td>
<td>Toe</td>
<td>Finger</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3.5 (0.3)*†</td>
<td>4.2 (0.1)*†</td>
<td>2.1 (0.4)*†</td>
<td>3.0 (0.3)*†</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>3.4 (0.4)*‡</td>
<td>4.2 (0.2)*‡</td>
<td>2.1 (0.4)*‡</td>
<td>3.1 (0.3)*‡</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>3.9 (0.3)‡</td>
<td>4.4 (0.1)‡</td>
<td>3.2 (0.1)‡</td>
<td>3.9 (0.2)‡</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.6 (0.0) †</td>
<td>4.8 (0.0) †</td>
<td>4.3 (0.1) †</td>
<td>4.4 (0.1) †</td>
</tr>
</tbody>
</table>

Averages were determined by calculating the areas under the decrease in PR versus time curves (AUC) and dividing by 120 min (duration of testing period after each dose). Values in parentheses are SEM.

Compared with placebo at same "dose" and site; *$P < 0.01$; †$P < 0.05$.

Compared with baseline: $P < 0.01$ (paired t tests) for all, including placebo.

Compared with placebo, changes from baseline: †$P < 0.01$; §$P < 0.05$.
after placebo was minimal. Decrement in time-averaged pain reports after fentanyl and alfentanil were significantly greater than after placebo for both small and large doses at both sites (finger and toe). Time-averaged pain reports after the small sufentanil dose were not significantly different from placebo, but after the larger dose, time-averaged toe pain report decreased significantly more than placebo (paired t tests; P values in table 2).

None of the subjects experienced any motor weakness. Sensory hypalgesia to pinprick was noted in four subjects, and hypesthesia to cold was noted in two subjects. In all cases, subjects could determine that sensory stimuli were sharp and cold, respectively, but they rated both ice and pinprick stimuli as "less cold" or "less sharp" than reference stimuli. When sensory changes were present, the dermatomal distribution of these changes was limited, ranging from one to three dermatomes, generally between T10 and L2.

**Ventilatory Effects**

Ventilatory drive measurements were performed at 30 min after epidural drug administration, the time previously reported for peak analgesia as well as peak plasma opioid concentrations. An additional ventilatory drive measurement was performed at 3 h after the second (larger) epidural drug doses. ETCO2 and V̇E,55 calculated from the hypercapnic ventilatory response curves are shown in figure 2. Mean ETCO2 did not increase significantly after the small doses of all three opioids, whereas increases of 10.1% (±2.1%), 10.4% (±2.0%), and 5.9% (±2.0%) were observed after the large doses of fentanyl, alfentanil, and sufentanil, respectively. Mean ETCO2 remained constant throughout the placebo study day. Significant overall drug (P < 0.05) and dose (P < 0.05) effects, as well as drug × dose interactions (P < 0.01) were detected by ANOVA. Follow-up paired comparisons revealed significant differences for each of the three opioids versus placebo (all P < 0.01) but no significant differences among opioids. There was no decrease in mean V̇E,55 after the small doses of all epidural opioids. After the larger epidural opioid doses, mean V̇E,55 decreased by 27.1% (±3.8%), 26.6% (±5.6%), and 25.1% (±6.1%) for fentanyl, alfentanil, and sufentanil, respectively. Significant overall differences were indicated by dose (P < 0.001) effects and drug × dose (P < 0.01) interactions. Paired comparisons revealed significant differences for each opioid versus placebo (all P < 0.02) but no significant differences among opioids. No changes in ETCO2 or V̇E,55 were seen after placebo doses. Depression of ventilatory drive resolved approximately 3 h after the large doses of each opioid.

**Nonrespiratory Side Effects**

We measured pupil size as well as subjective side effects (sedation, nausea, and pruritus) immediately after each analgesia assessment. Figure 3A displays the mean pupil size measurements throughout each study period.
We quantified sedation as a decrease in VAS rating of alertness. The alertness VAS scores showed slight decreases after the smaller epidural doses of all drugs that were comparable to control (placebo). A greater and more definite decrease in alertness was observed after the large opioid doses (fig. 3B). The mean alertness scores over the 2-h period after the small dose decreased from baseline scores by 21% (±7%), 23% (±6%), 25% (±6%), and 17% (±5%) for fentanyl, alfentanil, sufentanil, and placebo, respectively. Mean alertness scores over the 2-h period after the large dose averaged 53% (±6%), 48% (±7%), 30% (±8%), and 9% (±13%) lower than baseline scores for fentanyl, alfentanil, sufentanil, and placebo, respectively. Overall, drug effect ($P < 0.01$) and drug $\times$ dose interactions ($P < 0.05$) were significant, but paired comparisons did not reveal significant differences among the study opioids. Thus, the significant interactions represent differences between the study opioids and placebo.

Although most individual subjects did not experience nausea, some who reported nausea gave fairly high VAS scores. Table 3 displays the number of subjects who reported a significant degree of nausea (VAS score ≥ 20) after small and large epidural opioid doses. One subject reported nausea after 300 µg, and four reported nausea after 1,000 µg alfentanil. Two subjects reported nausea after 30 µg fentanyl, and the same two reported nausea after 100 µg fentanyl. Two subjects reported nausea after 3 µg sufentanil. Frequency of nausea was significantly different ($P < 0.05$, Cochran's Q test) only for overall comparison of high doses of all three opioids. Follow-up paired comparisons that have low power showed no significant paired differences.

The VAS scores for pruritus also showed a skewed distribution like that for nausea. Table 3 displays the number of subjects who reported a significant degree of pruritus (VAS score ≥ 20) after small and large epipipidural doses.

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**Table 3. Number of Subjects out of 12 with VAS Scores ≥20 for Nausea and Pruritus**

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Alfentanil</th>
<th>Sufentanil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small dose</td>
<td>2 (21–22)</td>
<td>1 (72)</td>
<td>2 (21–26)</td>
<td>0</td>
</tr>
<tr>
<td>Large dose</td>
<td>2 (70–80)</td>
<td>4 (51–90)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small dose</td>
<td>3 (20–73)</td>
<td>1 (47)</td>
<td>2 (26–48)</td>
<td>0</td>
</tr>
<tr>
<td>Large dose</td>
<td>5 (23–71)</td>
<td>4 (23–65)</td>
<td>4 (20–32)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values in parentheses are the range of peak scores for those subjects who reported VAS scores ≥20.

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dural opioid doses. Three subjects reported pruritus after 30 μg and five after 100 μg fentanyl. One subject experienced pruritus after 300 μg and four after 1,000 μg alfentanil. Two subjects also reported pruritus after 3 μg and after 10 μg sufentanil (peak scores). Frequency of pruritus was not significantly different across drugs for small or large opioid doses.

Because the frequencies of nausea and pruritus were low, it was difficult to determine whether these side effects were consistent across drugs. Both subjects with nausea after 100 μg fentanyl also had nausea after 1,000 μg alfentanil. The two subjects with nausea after sufentanil did not report nausea after the other opioids. One subject reported pruritus after all three opioids, and two subjects had pruritus with two of the three opioids (different combinations). We could not identify statistically any consistency of nausea across opioids. We found that, after the small epidural doses, pruritus was consistent across subjects (Kendall's W = 0.62, P = 0.04) but not after the larger doses (P = 0.20).

**Plasma Opioid Concentrations**

The time courses of plasma opioid concentration after small and large epidural doses of each of the three opioids are shown in figure 4. Horizontal broken lines indicate minimum effective plasma analgesic concentrations (MEACs) previously reported for these opioids after systemic administration. After the smaller epidural doses of all three opioids, plasma drug concentrations were well below MEACs. The mean peak plasma concentration of fentanyl was 0.19 ± 0.08 ng/ml. The time to peak concentration varied between 10 and 30 min after 30 μg epidural fentanyl. Plasma fentanyl concentration decreased to 0.11 ± 0.08 ng/ml by 2 h after administration. Alfentanil concentrations were less variable than the other two opioids. After the 300-μg dose, alfentanil was detectable in plasma within 1–5 min. Plasma alfentanil concentration reached a peak of 5.38 ± 1.97 ng/ml at 60 min. Likewise, very low plasma sufentanil concentrations were attained (<0.005 ng/ml) after the 3-μg dose; in many cases, it was undetectable.

Plasma opioid concentrations after the larger epidural doses of each opioid were near respective MEACs. After the 100-μg dose of epidural fentanyl, a mean peak plasma concentration of 0.36 ± 0.05 ng/ml was reached in 15 min. After 1,000 μg alfentanil, mean peak plasma concentration of 26.07 ± 2.04 ng/ml was reached early, at 15 min after epidural administration. Plasma alfentanil concentration gradually decreased to 6.53 ± 1.01 ng/ml by 3 h. After 10 μg epidural sufentanil, mean peak plasma concentration reached 0.035 ± 0.004 ng/ml at approximately 5 min after administration.

**Discussion**

The main purpose of this study was to characterize the pharmacokinetics and pharmacodynamics of epidural fentanyl, alfentanil, and sufentanil after two sequential bolus doses of each drug. We chose doses

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based on equianalgesic potencies for systemic administration but found that the 10:1 intravenous potency ratio (sufentanil 10 times as potent as fentanyl) did not apply to epidural administration. At the doses used in this study, we found nearly identical analgesic and side effect profiles for epidural fentanyl and alfentanil but significantly less analgesia after sufentanil. It is possible that sufentanil is so lipophilic that it is sequestered in epidural fat, and less is available for arachnoid mater to reach the site of action in the spinal cord. This is consistent with *in vitro* findings of Bernard and Hill, who reported that the octanol:buffer distribution coefficient for sufentanil was well outside the range of optimal meningeal permeability. Chrubasik et al. suggested starting epidural patient-controlled analgesia doses of 100 μg alfentanil, 10 μg fentanyl, and 3 μg sufentanil, because these doses had been found empirically to produce similar pain reduction. Such dose equivalents are similar to epidural potency ratios we would predict using observations from the current study, e.g., our small sufentanil dose would be roughly equivalent to one-third of the small doses of alfentanil and fentanyl.

Another purpose of this study was to clarify whether the characteristics of analgesia achieved in a laboratory setting were consistent with a localized spinal mechanism of action for these epidural opioids. If the epidural opioid were confined to the spinal segments subserving lumbar dermatomes, we would expect to find selective analgesia of the lower extremity, little or no upper-extremity analgesia, no supraspinal side effects, such as respiratory depression, pupillary constriction, and sedation, and plasma opioid concentrations well below MEAC for each opioid. The fact that upper-extremity analgesia and prominent supraspinal effects were observed indicates a significant redistribution of the epidural opioid to the brain, via rostral spread in CSF, absorption into the systemic circulation, or a combination of these two mechanisms.

For all three opioids, reduction in pain report was greater for the lower versus upper extremity. This observation suggests that there is a selective spinal action. Unlike epidural morphine analgesia, the onset of upper-extremity analgesia did not lag behind lower-extremity analgesia. Thus, it appears that rostral spread of spinal analgesia, although less extensive with epidural fentanyl and its derivatives, occurs rapidly. This interpretation is consistent with CSF fentanyl pharmacokinetics reported by Gourlay et al., who measured lumbar and cervical CSF concentrations after lumbar epidural administration. Peak cervical CSF fentanyl concentration, 10% of peak lumbar CSF concentration, occurred as early as 10 min after administration. Little is known about expected CSF concentrations after lumbar epidural administration of alfentanil and sufentanil in humans, but available animal data are similar to Gourlay's findings for fentanyl in humans. In dogs, Stevens et al. found that, after a large lumbar epidural sufentanil dose, peak cisternal CSF sufentanil concentration was only 2% of lumbar CSF peak, and maximum cisternal CSF concentration was measured within 20 min.

If analgesia were mediated only by systemic redistribution, we should have observed plasma opioid concentrations near or above reported MEACs. However, throughout the 2 h after the smaller epidural dose of each opioid, we measured extremely low plasma concentrations. In addition, epidural fentanyl and alfentanil produced toe analgesia greater than we would have predicted based on systemic opioid studies. In our previous studies of systemic opioid analgesia, we employed electrical tooth pulp stimulation to compare analgesic effects of steady-state morphine, fentanyl, and alfentanil in normal volunteers. Using the same numeric scale for analgesia (reduction of pain report on a 0–5 scale), we found that mean pain reports of 3.4–3.5 were associated with 0.75 ng/ml fentanyl and 40 ng/ml alfentanil. Gourlay et al. reported a fentanyl MEAC for postoperative analgesia of 0.6 ng/ml, with a wide interpatient variation (0.2–1.2 ng/ml). Lehmann reported a MEAC of 10–15 ng/ml for alfentanil, but in that study, blood samples were drawn just before patients' requests for bolus doses; therefore, the estimated MEAC is probably too small. van den Nieuwenhuyzen et al. estimated MEAC for alfentanil between 43 and 65 ng/ml. In the current study, toe pain reports of 3.5 and 3.4 (table 2) were achieved at maximum plasma opioid concentrations of 0.19 and 5.38 ng/ml after epidural fentanyl and alfentanil, respectively. Thus, epidural fentanyl and alfentanil achieved nearly identical reductions in pain report with three-to-fivefold lower plasma drug concentrations as compared to those achieved during steady-state intravenous infusion and much lower than reported MEACs. Although dental and cutaneous stimulation are not identical pain models, Pavlin et al. conducted a study in our laboratory using the finger-shock model with steady-state alfentanil infusions that were targeted to plasma concentration similar to that in our earlier intravenous study. Pain reports very similar to those ob-
tained with the tooth-shock model were observed at similar plasma alfentanil concentration. Overall, the lower-extremity selectivity and the similar magnitude of analgesia achieved at much lower plasma opioid concentration during epidural compared to systemic administration of fentanyl and alfentanil support direct spinal action. The absence of supraspinal effects, pupil constriction, sedation, and ventilatory depression after the small epidural doses of fentanyl and alfentanil is consistent with a spinal mechanism of action. Because the smaller epidural sufentanil dose used in this study did not produce analgesia significantly different from placebo, comparison of the side effects here is not meaningful.

The role of systemic opioids in analgesic and side effects observed after larger epidural doses is more difficult to interpret. One complicating factor is that the effects of the smaller doses had not resolved completely at the time of the larger dose administration. In addition, plasma opioid concentrations were still detectable before the second (larger) doses. For all three opioids, peak plasma concentrations approached reported MEACs. Again, finger and toe analgesia reported after the larger epidural doses can be compared with analgesia produced by steady-state intravenous opioid infusions during dental stimulation. During intravenous opioid infusions that achieved a plasma fentanyl concentration of 1.5 ng/ml and an alfentanil concentration of 80 ng/ml, dental stimulation elicited pain reports of 2.3–2.5. In the current study, toe pain reports of 2.1 were associated with 0.36 ng/ml fentanyl and 26.07 ng/ml alfentanil. Thus, at comparable dental and toe pain report scores, plasma fentanyl and alfentanil concentrations after epidural administration were two- to threefold lower than during intravenous administration and 50–60% of reported MEACs from clinical studies. It is unlikely that systemic redistribution alone can account for the magnitude of toe analgesia achieved after these epidural doses, and therefore, a direct spinal mechanism is likely responsible for most of the lower-extremity analgesia. These findings contrast with finger analgesia measurements. At comparable finger and dental pain report scores, plasma fentanyl and alfentanil concentrations after epidural administration were about half the plasma concentrations measured during intravenous infusion. Although limited local spread of epidural opioid (as has been reported for fentanyl) would be consistent with less finger analgesia, one cannot eliminate the possibility that systemic presence of the opioid is contributing to upper-extremity analgesia.

Epidural sufentanil produced less analgesia than did epidural fentanyl and alfentanil at both sites, and results can be compared to our study of systemic analgesia during steady-state intravenous sufentanil and morphine infusions. At plasma sufentanil concentrations similar to those achieved with intravenous administration, epidural sufentanil produced decrements in pain reports comparable to those seen with dental stimulation. The MEAC for sufentanil is not well established. Like the reported alfentanil MEAC, Lehmann’s estimate of sufentanil MEAC of 0.024 ng/ml is likely to be low. Geller et al. noted mean plasma sufentanil concentrations as low as 0.04 ng/ml during postoperative intravenous infusions. Toe analgesia greater than finger analgesia suggests a spinal mechanism. However, the similar magnitude of maximum analgesia observed with intravenous and epidural administration and peak plasma sufentanil concentration greater than 0.05 ng/ml after epidural administration suggest that much of the analgesia achieved with sufentanil can be attributed to systemic redistribution. After the large epidural doses of all study opioids, we observed significant supraspinally mediated side effects (increased $etCO_2$, $V_{E55}$, sedation, and pupil constriction). These findings are consistent with either systemic absorption or rostral spread in CSF and probably represent a combination of both mechanisms. They also suggest that supraspinal side effects of epidural sufentanil might be greater than those of epidural fentanyl and alfentanil at equivalent analgesic doses, but further studies are necessary to confirm this impression.

Several investigations have attempted to determine the site of analgetic action of epidural fentanyl, alfentanil, and sufentanil by comparing analgesia and plasma opioid concentrations in postoperative patients receiving infusions of fentanyl by either the intravenous or the epidural route. In all trials, opioids were titrated to adequate pain relief and analgesic mechanism was inferred by comparing plasma opioid concentrations during epidural and intravenous administration providing equal analgesia. Two investigators reported equivalent plasma fentanyl concentrations, whereas others found lower plasma drug concentrations with epidural fentanyl up to 18 h after opioid administration. Camu et al. found lower plasma alfentanil for the first hour with epidural compared to intravenous infusions of alfentanil, and Geller et al. noted lower plasma sufentanil concentrations during epidural compared to intravenous administration. Two basic study design characteristics appear to account for these dif-
ferences. If epidural catheter placement was near the expected dermatomal level of nociceptive input and either drug was titrated downward or patient-controlled bolus only (i.e., no infusion coadministered) was allowed, investigators found lower plasma opioid concentrations, at least during the first few hours, consistent with a selective spinal mechanism with epidural administration. However, although it appears possible to administer lipophilic epidural opioids in a way that suggests a selective spinal mechanism, none of these studies demonstrate overwhelming clinical advantages to administering these opioids via the epidural route. Furthermore, after 2–12 h, all studies reported plasma opioid concentrations near MEACs. One difference between clinical studies in surgical patients and our laboratory study is that experimental pain stimuli produce "strong pain" but are well within pain "tolerance." In clinical studies, pain is generally more severe. We found analgesia at both extremes as well as supraspinal side effects, including respiratory depression and sedation, with higher epidural doses. In clinical situations involving severe pain, it may not be possible to limit epidural doses to those that appear to produce selective spinal analgesia without supraspinal side effects.

Another difference between many clinical studies and our laboratory investigation is that, in the former, interactions between study opioids and other drugs, especially epidural local anesthetics, may have occurred. In this laboratory study, we tested for segmental sensory block with lidocaine after data collection was complete to avoid any possibility of opioid interaction with local anesthetics. However, epinephrine, given in this study to rule out intravascular catheter placement, can prolong the duration and intensity of epidural opioid analgesia possibly by decreasing vascular absorption from the epidural space. Potential adrenergic effects of epinephrine may not have resolved completely by 1 h after administration, and it is possible that subclinical effects of epinephrine contributed to the magnitude or duration of epidural opioid analgesia.

In summary, we compared effects of epidural fentanyl, alfentanil, and sufentanil in normal volunteers. We found that epidural sufentanil produces less analgesia but equivalent respiratory depression relative to fentanyl and alfentanil when intravenous potency ratios are considered. Its very high lipophilicity may limit epidural sufentanil's access to spinal sites of action. Although decreased epidural potency may be overcome by administering larger doses, such a practice might put patients who experience inadvertent intravenous administration, e.g., due to catheter migration into an epidural vein, at higher risk for serious complications including respiratory depression.

We found that epidural doses of fentanyl and alfentanil clearly provide selective lower-extremity analgesia. The very low plasma opioid concentrations after small epidural doses suggest a spinal mechanism of analgesia. However, larger doses result in systemic absorption and plasma concentrations near MEAC and are likely produce supraspinal analgesia and side effects. It is unlikely that systemic absorption and supraspinal effects can be avoided if clinical conditions require larger epidural doses of these opioids. Thus, whereas hydrophilic epidural opioids, such as morphine, have the disadvantage of producing supraspinal effects because of rostral spread in CSF, lipophilic epidural opioids produce similar supraspinal effects because of extensive systemic redistribution. Our findings support many clinical investigators' conclusion that, regardless of mechanism, epidural administration of these lipophilic opioids may offer no clinical advantage over the intravenous route. However, administration of small doses of lipophilic epidural opioids in combination with other drugs may offer an advantage over systemic administration. Potential candidates for combination include drugs that decrease systemic absorption of epidural opioids (e.g., vasoconstrictors) or those that provide spinal analgesia (e.g., $\alpha_2$-agonists or local anesthetics). More research comparing such combinations to intravenous administration is needed. In addition, studies comparing the analgesia measured during epidural versus intravenous administration that produced equivalent plasma opioid concentrations may be able to quantify the proportion of analgesia contributed by direct spinal and supraspinal mechanisms.

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