Equivalent Analgesia and Side Effects during Epidural and Pharmacokinetically Tailored Intravenous Infusion with Matching Plasma Alfentanil Concentration

Barbara A. Coda, M.D.,* Mary Cleveland Brown, R.N.,† Linda Risler, B.S.,‡ Karen Syrjala, Ph.D.,§ Danny D. Shen, Ph.D.‖

**Background:** Recently, several clinical studies comparing intravenous and epidural infusions of fentanyl and its derivatives suggested that epidural infusions act primarily by systemic absorption to produce supraspinal analgesia. To evaluate this hypothesis, the authors used pharmacokinetically tailored intravenous infusions to produce matching plasma alfentanil concentrations during epidural and intravenous administration. The analgesia and side effects achieved with each mode of administration were compared.

**Methods:** Twelve volunteers participated in this placebo-controlled crossover study. The pain model was cutaneous electric stimulation of the finger and toe. The test battery included subjective rating of pain intensity; end-tidal carbon dioxide level; pupil size; ratings of alertness, nausea, and pruritus; and a plasma alfentanil assay. On one test day, the participants received epidural alfentanil (400 µg bolus + a 400-µg/h infusion for 2 h) and an intravenous saline infusion. The test battery was administered at regular intervals. On another test day, the participants received epidural saline and a computer-controlled intravenous infusion of alfentanil. The testing protocol was repeated as on the first test day. On the day the placebo was administered, the participants received epidural and intravenous saline infusions. The order of the placebo day was randomized.

**Results:** Plasma alfentanil concentration–time profiles were identical during epidural and intravenous infusions. A nearly equivalent analgesic response was observed with epidural and intravenous alfentanil at the upper and lower extremities. There were no differences in side effects for epidural and intravenous administration.

**Conclusions:** The systemic redistribution of alfentanil accounts for most of the analgesia and effects produced by epidural infusion. (Key words: Analgesic techniques; epidural analgesic mechanism; spinal opioids.)

SEVERAL clinical studies in patients after surgery have evaluated the pharmacodynamic mechanisms of epidural opioids by comparing intravenous and epidural infusions of fentanyl,1–4 alfentanil,5,6 and sufentanil.7 The opioid dose was titrated to patient satisfaction, and therefore epidural and intravenous routes of administration both provided adequate and equivalent pain relief. A comparison of the total opioid dose required or plasma opioid concentrations suggested that epidural administration of fentanyl1,2,3 and its derivatives4,7 provides little advantage compared with intravenous infusions. Several studies have reported that fentanyl dose requirements were similar with both routes of administration,1,4 and the authors suggested that epidural fentanyl probably acted primarily by systemic absorption to produce analgesia. Camu and Debucquoq5 and Chauvin et al.6 reported equivalent analgesia and similar side effects with
epidural and intravenous alfentanil. Thus, epidural alfentanil appeared to provide little clinical benefit over intravenous alfentanil. In contrast, Chrubasik et al. reported that epidural alfentanil produced slightly greater pain relief with less sedation and smaller plasma opioid concentrations compared with subcutaneous alfentanil from 2 to 24 h after operation, and they concluded that epidural alfentanil produces analgesia through a spinal site of action.

We evaluated this hypothesis in healthy volunteers during tightly controlled laboratory conditions. Rather than titrate to equivalent levels of analgesia, we achieved identical plasma alfentanil concentrations during epidural and intravenous administration. Participants received epidural and intravenous alfentanil and placebo on separate study days in a single-blinded study design. We compared the analgesia achieved and the side effects that occurred to determine the extent of the contribution of systemic analgesia to the total analgesia achieved with epidural alfentanil. This experimental approach also allowed us to compare the sensory distribution of analgesia by applying painful stimuli to lower and upper extremities. Theoretically, only epidural infusion should provide primarily segmental analgesia, perhaps segmental side effects such as pruritus, and limited supraspinal side effects such as sedation and respiratory depression. Intravenous alfentanil with a matched plasma concentration should produce similar supraspinal effects and less analgesia, which would not be segmental in nature.

Methods

In this single-blinded, placebo-controlled crossover study, all volunteers participated in one prestudy session to pharmacokinetically tailor alfentanil and in three study sessions to compare the effects during epidural alfentanil, intravenous alfentanil, and saline infusion. The sessions were separated by at least 10 days. On one study day, the participants received epidural alfentanil. On a second study day, they received a pharmacokinetically tailored intravenous infusion designed to reproduce the plasma alfentanil concentration–time profile measured on the epidural study day. On a third study day, the participants received intravenous and epidural saline (placebo). The order of the placebo day was counterbalanced so an equal proportion of participants received placebo infusions on the first, second, and third epidural study days, but because of the requirements of the study design, the intravenous infusion day always followed the epidural infusion day.

Participants

Twelve healthy volunteers, 6 men and 6 women, aged 21–36 yr (mean, 25 yr) participated in the study. Body weight ranged from 55.2 to 101.2 kg (mean, 72.2 kg), and all participants were within ± 10% of normal weight for their height. One participant used oral contraceptives. No other participants were taking regular medications of any kind, and none reported any history of drug or alcohol abuse. All provided written informed consent as approved by the institutional review board of the Fred Hutchinson Cancer Research Center.

Experimental Pain Model

Pain was induced experimentally by cutaneous electric stimulation, which was delivered alternately to the finger (C7 or C8 dermatomal distribution) of the nondominant hand and to an ipsilateral second or third toe (L5 dermatomal distribution). For stimulus delivery, a 1-mm² area of skin was abraded with a dental burr, and a silver electrode was taped in place. On each day, we established the baseline stimulus–response relationship by gradually increasing the stimulus current and by having the participant rate the pain intensity of each stimulus by moving the pointer of a slide potentiometer along a continuous 5-cm scale. Word descriptions with numeric markers were included at regularly spaced intervals along the scale and corresponded from 0 = faint sensation, no pain; 1 = very faint pain (pain threshold); to 5 = strong pain. The participants moved the slide potentiometer to any position along the 5-cm scale to indicate the intensity of each stimulus. The stimulus current was increased gradually until a level was established that consistently produced a rating of 5. Once established, this level of stimulation intensity was maintained throughout the study day. The resultant pain sensation was very distinct, described as sharp, stabbing, and burning, and at higher intensities it was accompanied by a more diffuse aching sensation. Stimulus intensities necessary to elicit a rating of 5 were determined separately for the toe and the finger. These same stimulus intensities were used for the volunteers throughout that study day. Stimulus intensities were reestablished on each study day. Our experience with this technique over 7 yr has shown that the baseline stimulus–response relation for individuals remains stable during multiple study sessions (unpublished data).

A Grass model 44 stimulator (Quincy, MA) with constant current and stimulus isolation units produced repeating 5-ms square wave pulses of 0.5- to 2-mA intensities. The interstimulus interval varied from 4 to 6 s.
(average, 5 s). To ensure constant stimulus intensity, skin impedance was maintained within the range of 2 to 10 KΩ. Painful stimuli were delivered alternately to the toe and then to the finger in sets of 50 stimuli (25 at each site). The volunteers rated the intensity of each stimulus by moving the pointer of a slide potentiometer to any position along the continuous scale described previously. Data from the pain reports were averaged separately for the toe and finger at the end of each set of stimuli by the computer. Each stimulation set required approximately 5 min to be completed.

Cutaneous Sensory Change and Motor Strength

We determined the volunteers’ sensitivity to pinprick and to ice placed on the skin of the abdomen, thighs, and legs. The volunteers rated sharp and cold sensation compared with a reference point on the upper arm, and they graded the sensation as equal or less sharp or cold compared with 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, 4: movement against resistance, and 5: normal strength.

Ventilatory Effects

We defined respiratory depression as an elevation of resting end-tidal carbon dioxide level, which was measured while the participants were at rest and breathing through a nose mask, using a Hewlett Packard model 78356A carbon dioxide analyzer (Palo Alto, CA).

Pupil Size

We measured pupil size as an independent assessment of supraspinal opioid effect. We used a modified Essilor pupillometer (Essilor, France) as described by Ravnborg et al. After allowing 15 to 20 s for adaptation to the pupillometer light source, we recorded the maximum pupil diameter measured during a 10-s observation period.

Subjective Side Effects

The participants rated the intensities of side effects using 100-mm visual analog scales (VASs) for nausea, pruritus, and alertness. Nausea and pruritus scales were anchored by “none” and “worst possible” descriptors, and the alertness scale was anchored by “can’t keep my eyes open” and “wide awake” descriptors.

Prestudy Pharmacokinetic Tailoring

At least 1 week before the first study day, the participants received 15 µg/kg intravenous alfentanil hydrochloride infused over 3 min and followed by a 10-ml normal saline flush. We collected venous blood samples before drug administration and 1, 2, 3, 4, 5, 7, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min after drug administration to measure plasma alfentanil concentrations. Blood samples were maintained on ice until the end of the day, when they were centrifuged and the plasma was frozen at –20°C for later assaying.

We fitted a bi- or triexponential equation (Cp = Ae⁻αt + Be⁻βt or Cp = Pe⁻αt + Ae⁻βt + Be⁻γt, respectively) to the resultant plasma alfentanil concentration-versus-time data of each participant using a nonlinear least-squares regression computer program (RSTRIP, MicroMath, Salt Lake City, UT). The exponential function that provided the better fit, based on the weighted sum of squared residuals and Akaike’s criterion, was selected for each participant as the appropriate pharmacokinetic model for use in subsequent tailored infusions. Details of our pharmacokinetic tailoring methods and the computer-driven infusion pump system have been reported previously. For computer-controlled infusions of alfentanil, we reported a mean absolute prediction error of 15.9% during infusions lasting 1 to 3 h in healthy volunteers and of 33.6% for infusions lasting as long as 2 weeks in patients undergoing bone marrow transplants.

Study Sessions

The volunteers fasted after midnight before each study day and refrained from consuming alcohol or taking any medications for 24 h before each study day. A urine pregnancy test (HCG-Urine CARDS; Pacific Biotech, San Diego, CA) was performed on the morning of each study session for all female volunteers. Each session occurred in a sound-attenuated chamber with the volunteer seated in a hospital bed. At the beginning of each study day, a 20-gauge intravenous catheter was placed in one arm for study drug and fluid administration, and an 18-gauge catheter was placed in a vein of the opposite arm for serial blood sampling. Baseline measurements were collected for the pain report, sensory and motor function, subjective side effects, end-tidal carbon dioxide level, and pupil size. After baseline measurements, the volunteers assumed a left lateral decubitus position, and an Arrow FlexTip Plus epidural catheter (Arrow International, Reading, PA) was placed at the L2-3 or L3-4 interspace via a 17-gauge Weiss needle using a midline approach, and was advanced 2.5 to 3 cm into the epidural space. A test dose of 2 ml of air with precordial Doppler monitoring was used to rule out intravascular...
Epidural and IV Alfentanil in Volunteers

At the end of each study day, epidural catheter placement was confirmed using 3 to 5 ml of epidural lidocaine, 1.5%, with 1,200,000 epinephrine to obtain a dermatomal distribution of sensory blockade. Confirmation with local anesthetic was performed at the end of the day to avoid a potential interaction between the local anesthetic, even at subclinical doses, and the study opioid.

On one study day, approximately 30 min after the air test dose, the volunteer received an epidural loading dose of 400 µg alfentanil hydrochloride (368 µg alfentanil base) diluted to a volume of 6 ml in preservative-free normal saline. The dose was infused over 5 min and was followed by a 2-h epidural infusion of alfentanil hydrochloride at 400 µg/h in a volume of 10 ml/h. This regimen was chosen to approximate clinical practice, which generally includes a “loading” dose followed by a maintenance infusion. At the same time, a computer-controlled intravenous infusion of saline was started and then maintained for 4 h. The test battery was administered at baseline and at time points beginning at 5, 60, 90, 120, 180, and 240 min after the start of the alfentanil administration. Serial blood samples (7 ml each) were collected before and 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210, and 240 min after the start of the alfentanil administration and kept on ice until the end of the study day for a later alfentanil assay.

At the start of a second study day, intravenous and epidural catheters were placed in the exact manner as on the first study day. After baseline measurements, we infused an epidural dose of 6 ml of preservative-free saline over 5 min, followed by a saline epidural infusion at 10 ml/h. At the same time, we started the pump system to deliver the pharmacokinetically tailored intravenous infusion regimen of alfentanil designed to match the plasma alfentanil concentration–time profile measured on the epidural study day. To achieve this, we plotted the plasma alfentanil concentration–time data from the epidural study day and visually approximated the curve by a series of stepwise increases or decreases in concentration that varied in duration (see Fig. 1 for an example). On the intravenous alfentanil study day, we entered the initial target plasma concentration (first step) and the participant’s pharmacokinetic parameters determined on the prestudy day into a computer. The computerized pump system consisted of a Toshiba 1000 microcomputer (Tokyo, Japan) connected to the RS-485 port of an Abbott LifeCare model 4 infusion pump (Abbott Park, IL) that was programmed to calculate and deliver a loading dose and time-variant infusion rate to rapidly reach and maintain the target concentration. At the predesignated time for each subsequent step change in concentration, we manually activated a switch to increase or decrease the target plasma concentration. The testing sequence for analgesia, side effects, and blood sampling was identical to that followed on the first study day. The target concentrations and durations for plateaus of the intravenous infusion differed among the participants, but the total duration of intravenous infusion was the same (4 h) for all participants. In one of them, the tailored infusion produced plasma alfentanil concentrations 30% less than the desired target, and this infusion was repeated using revised targets adjusted to account for the underdosing.

On a third study day (the placebo day), epidural and intravenous catheters were placed as on the previous days. After baseline measurements, an epidural bolus dose and infusion and a variable-rate intravenous infusion of saline were administered. The testing sequence and blood sampling were then performed in the same manner as on the other two test days. The order of this placebo session was randomized. Because the study design necessitated that epidural alfentanil was always administered before intravenous alfentanil, the investiga-

Fig. 1. A representative plasma concentration–time profile from an epidural study day in one participant, and an illustration of the concentration steps chosen for the tailored intravenous alfentanil infusion. Open circles indicate the measured plasma alfentanil concentration after epidural administration of a 400-µg epidural loading dose followed by a 400-µg/h epidural infusion of alfentanil. The dotted lines represent the series of concentration steps selected as targets for the tailored intravenous infusion day for this participant. The choice of targets and the duration of each step was made by visual inspection of the alfentanil concentration versus time graph.
itors could not be blinded. The participants were told that they would receive alfentanil by both routes and a placebo, but they did not know the order of treatments (they were blinded to treatment order).

All but one of the epidural catheters were placed on the first pass. All participants experienced typical segmental sensory blocks extending two to four dermatomes 15 to 20 min after the local anesthetic was administered.

**Plasma Alfentanil Assay**

Plasma alfentanil concentrations were determined by gas chromatography–mass spectrometry using a modification of the method of Woesenborghs et al. This method consists of a multiple-step liquid–liquid extraction of plasma and gas chromatography–mass spectrometry analysis of the extracts using a DB150 capillary column (J&W Scientific, Folsom, CA). An internal standard (R38,527; Janssen Biotech H.V., Olen, Belgium) was used to correct for drug recovery throughout the extraction and analytical process. Pseudomolecular ions for alfentanil and the internal standard, 289 and 282 m/z, were monitored. The detection limit was 0.1 ng/ml, with an interday coefficient of variation of 9.9% at 20 ng/ml.

**Statistical Analysis**

Analyses were performed using the SPSS for Windows statistical package (Chicago, IL). First, we inspected primary outcomes for normality of distribution and homogeneity of variance to ensure the necessary assumptions were met for the use of analysis of variance (ANOVA) procedures. Next, we evaluated the accuracy of intravenous infusions in reproducing plasma concentrations. Inspection of the means, standard deviations, normality of distribution, and variances of the measures within each time point indicated the expected restricted distribution of scores for the baseline and first minute of testing for plasma concentration, pain, and side effects. From 3 min after the start of infusions until 240 min, the distributions were relatively normal and variances were relatively homogeneous, meeting the criteria for ANOVA assumptions. Therefore, although all data are presented for visual inspection in graphs, the time window of 3 to 240 min was used for ANOVA group comparisons. We evaluated the accuracy of intravenous infusions in reproducing plasma concentrations measured on the epidural day by visual inspection of graphs comparing plasma concentration versus time. For the time interval from 3 to 240 min (as just described), we compared plasma concentrations across time and between epidural and intravenous infusions with repeated-measures ANOVA. Then we evaluated outcome variables for analgesia and side effects by graphing each effect measure (e.g., the pain report at each testing site, pupil size, alertness) versus time.

After analysis of plasma concentrations, we analyzed the main effects and interactions of time and infusion conditions (epidural, intravenous, or placebo) with repeated-measures ANOVA for the 3- to 240-min time period. Post hoc analyses for those comparisons showing significant interactions among more than two groups were performed using the Scheffé test. For the pain report, we tested segmental analgesia by comparing epidural with intravenous infusion for toe versus finger stimulation. We analyzed differences among the three infusion conditions versus time for analgesia. For side effects, we evaluated the three infusion conditions for three effects (pupil size, end-tidal carbon dioxide level, and alertness). Because our goal was to determine whether the infusion groups were equivalent (to accept the null hypothesis), the most conservative approach to multiple outcomes testing was not to apply Bonferroni corrections. Therefore, we did not correct for multiple outcomes testing. For nausea and pruritus, we determined the number of times each volunteer reported the symptom during the 4-h infusion. We defined the presence of each as a VAS rating of ≥20 mm for two or more time points. Then we compared frequencies among groups using McNemar’s test. We accepted a P value of 0.05 as an indication of a significant difference among the groups.

**Results**

**Plasma Alfentanil Concentrations**

At visual inspection, we found that the plasma alfentanil concentration–time profiles of pharmacokinetically tailored intravenous infusions matched those observed during epidural administration (figs. 2 and 3). The total doses of alfentanil on the epidural and intravenous days were similar: 1,200 μg (exactly) and 1,124 μg (100 μg SEM) for epidural and intravenous days, respectively. Plasma alfentanil concentrations generally reached plateau levels between 10 and 20 ng/ml (fig. 3), which is between the minimum effective analgesic concentration ranges reported by van den Nieuwenhuyzen et al. (40 ng/ml) and Lehmann (10–15 ng/ml). Repeated-measures ANOVA found no main effect of route of administration (intravenous vs. epidural infusion) or plasma con-
Epidural and IV Alfentanil in Volunteers

Fig. 2. A comparison of the mean plasma alfentanil concentration-time data between the epidural and tailored intravenous infusion days. Values are the mean (± SEM) for 12 participants on epidural (open circles) and tailored intravenous (filled circles) study days.

Centrations over time (F = 0.47, P = 0.507). As expected, a main effect of time on infusion was seen (F = 23.61, P < 0.001). Furthermore, we saw a significant interaction of time by type of infusion (F = 3.23, P < 0.001). Post hoc analysis showed that the plasma concentration was greater for the epidural route at onset (3 and 5 min) and greater for the intravenous route at the 60-min time point. No other comparisons across the 18 tested times for epidural versus intravenous route approached significance (all P > 0.2).

Analgesia
For epidural and intravenous alfentanil, the onset of analgesia was rapid, and maximum analgesia was measured at approximately 15 min (fig. 4). At visual inspection, we saw no segmental analgesia with epidural or intravenous alfentanil administration (fig. 4) and no analgesia with placebo. Repeated-measures ANOVA comparison of analgesia among the three routes (epidural, intravenous, and placebo) found an expected main effect for condition (F = 17.99, P < 0.001). Post hoc analyses indicated significantly less analgesia, with placebo infusion at 12 of 16 time points (P ≤ 0.001); differences were not significant at 4 min (i.e., near onset) and from 177 to 240 min, indicating that analgesia had resolved by then. However, pain reports did not differ significantly at any time in post hoc comparisons of epidural and intravenous infusions. Comparison of finger and toe analgesia revealed no main effect of stimulus site (F = 0.22, P = 0.644) and no interaction of time with stimulus location (F = 0.13, P = 1.00). As expected, there was a significant main effect of pain report versus time (F = 25.61, P < 0.001). We noted a segmental decrease in sensitivity to pinprick in five volunteers with epidural administration, but the dermatomal distribution was limited, and all were between T10 and L2. Two participants reported hypesthesia to cold that was limited to the L1 and L2 dermatomes. No participant experienced any motor weakness.

Side Effects
Mean end-tidal carbon dioxide level did not change significantly on any of the study days (fig. 5A). Oxygen saturation remained greater than 97% (while breathing room air) for all participants. Pupil size decreased by a similar amount during intravenous and epidural alfentanil infusion, but no change occurred during placebo administration (fig. 5B). The mean alertness VAS scores decreased markedly with both epidural and intravenous alfentanil and only slightly during placebo administration (fig. 5C). Repeated-measures ANOVA compared end-tidal carbon dioxide level, pupil size, and alertness between the epidural and intravenous infusion routes. For the end-tidal carbon dioxide level, no significant main effects for time or route (P = 0.34, P = 0.42, respectively) were seen. Furthermore, no interaction occurred for time by route. Pupil size and alertness both changed significantly with time (P < 0.001). However, we found no main effect for infusion route or any interaction between time and route (P = 0.25 to 0.72).

For nausea and pruritus, we defined an occurrence of the side effect when a VAS score of 20 mm or more on a 100-mm VAS scale was reported for at least two time points during the 4-h study period. Table 1 displays the frequency and severity (shown as peak score) of these side effects. Nausea was infrequent; two volunteers reported nausea that met these criteria during the epidural study day and one reported this on the intravenous study day (P = 1.00 by McNemar’s test). Several volunteers reported nausea at only one time point with both methods of administration, but in all of these cases peak scores were less than 30. Two volunteers experienced pruritus when they received epidural alfentanil, and these same two persons plus three additional volunteers reported pruritus with intravenous administration of alfentanil. These frequencies were not significantly different (P = 0.25 by McNemar’s test). Peak VAS scores for pruritus tended to be higher with intravenous compared with...
CODA ET AL.

Fig. 3. Matching of alfentanil concentration with time in 12 participants during epidural (open circles) and tailored intravenous (filled circles) infusions. The dotted lines indicate the target concentration profile for each participant. (The target profile is not indicated for participant 10 because that infusion was repeated with modified targets; see text for details.)

epidural alfentanil, but the difference was not statistically significant. No volunteers reported nausea or pruritus on the days the placebo was administered.

Power analysis showed that with data from the 12 volunteers, and given the standard deviations in this sample, we had more than 80% power to accept the null hypothesis for analgesia, end-tidal carbon dioxide level, and alertness.

Discussion

This study was designed to determine whether epidural alfentanil produces analgesia by a localized spinal mechanism. If epidural alfentanil acted only at the spinal segments subserving lumbar dermatomes, we should find selective analgesia of the lower extremity only. Conversely, during intravenous administration, we would predict that analgesia would be equal at the upper and lower extremities. We found no difference between upper and lower extremity analgesia and no differences in the magnitude and time course of analgesia with either route of administration. Possible explanations for these findings include rapid, extensive spread in the epidural space or systemic absorption from the epidural space and redistribution to supraspinal and spinal sites of action.

We could not measure epidural drug concentrations, but such measurements have been performed in ani-

Anesthesiology, V 90, No 1, Jan 1999
Fig. 4. The time course of the mean pain report for fingers (filled triangles) and toes (open triangles) during the (A) epidural, (B) intravenous, and (C) placebo study days. The pain report at each time point is the average of 25 stimulus trials at each site. Values are the mean (± SEM) for 12 participants.

Fig. 5. The time course of the mean side-effect measures during the epidural alfentanil (open circles), intravenous alfentanil (filled circles), and placebo (open triangles) infusions. (A) The mean end-tidal carbon dioxide pressure during the three study days. (B) The mean pupil size, measured using a modified Essilor pupilometer. (C) Subjective alertness ratings. Alertness values were measured with a 100-mm visual analog scale anchored by “wide awake” and “can’t keep my eyes open” criteria. For all three side effects, changes from baseline were significant for both routes (P < 0.01, Student’s t tests), but no significant difference was seen between epidural and intravenous alfentanil administration. All values are the mean (± SEM) for 12 participants.
Table 1. Number of Subjects of 12 Who Reported Significant Nausea or Pruritus, Defined as VAS Scores ≥20 at Two or More Time Points

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Epidural</th>
<th>Intravenous</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2 (26-63)</td>
<td>1 (77)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (38-59)</td>
<td>5 (30-78)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values in parentheses are the range of peak scores for subjects reporting nausea and pruritus.

Fentanyl and sufentanil, do not readily gain access to spinal cord tissue after epidural administration, but rather tend to become sequestered in epidural fat and cleared via the circulation. Lipid solubility is intermediate with alfentanil, but this drug has the greatest barrier permeability. It partitions into epidural fat to some extent but enters epidural arteries more rapidly than do fentanyl and morphine after epidural administration. Alfentanil also readily accesses the spinal cord, but the concentration in the cord tissue remains low because of its avid vascular uptake (C. Bernards, personal oral communication, February 1998). This suggests that direct spinal analgesia is minimal, and systemic absorption is likely to account for most of the analgesia observed with the epidural administration of alfentanil.

The results of this study differ somewhat from those of a pilot study in which 750 μg alfentanil was administered as an epidural bolus dose. In that study, we found greater toe analgesia with epidural alfentanil, but only during the first hour after the bolus. However, epidural bolus administration produced peak plasma alfentanil concentrations of 20 and 40 ng/ml, approximately twice the maximum concentrations of 12 to 18 ng/ml that we found in the current study. Perhaps a large concentration gradient is necessary to facilitate diffusion from the epidural space across the cerebrospinal fluid to a spinal site of action. It could be argued that, in this study, the epidural alfentanil did not reach the sacral distribution, a possibility supported by the evidence of limited dermatomal sensory changes. However, unlike local anesthetics that require distribution to sacral nerve roots to provide local anesthesia or analgesia by conduction blockade, epidural opioids must reach the dorsal horn of the spinal cord to reach the spinal opioid receptors. Because the spinal cord terminates between T12 and L2 in adults, administration at the L2-3 or L3-4 interspaces would reach the spinal cord level, subserving sacral dermatomes before reaching the lumbar dermatomes. In the case of spinal sufentanil administration, sensory changes to pinprick and cold do not predict analgesia, but similar studies with alfentanil have not been performed.

The lack of difference between lower and upper extremity analgesia observed in the current study contrasts with the findings of another study from our laboratory, in which volunteers received two successive epidural bolus doses (300 and 1,000 μg) of alfentanil. In that study, low-dose epidural alfentanil produced analgesia selective for the lower extremity, despite very low plasma alfentanil concentrations (<10 ng/ml). One possible explanation for this discrepancy is that we used a test dose of epinephrine to rule out intravascular placement of the epidural catheter at the beginning of the study day. A recent clinical investigation showed that the addition of 1,500,000 epinephrine to an epidural fentanyl infusion decreased plasma fentanyl concentrations and reduced the fentanyl dose requirement for effective analgesia. Possible mechanisms include limited vascular uptake from the epidural space, which could facilitate drug distribution to the spinal cord, or direct activation of spinal α2-adrenoceptors by epinephrine.

Decreases in pupil size and alertness, both of which reflect supraspinal effects, were identical over time for both methods of administration. These results were expected because of the study design, which matched plasma opioid concentrations, and resultant drug delivery to the brain via the systemic circulation. Pruritus, which may be mediated by a spinal mechanism, was also similar with both routes of administration.

Our findings contrast with those of Penon et al., who reported analgesia and respiratory depression with epidural alfentanil only. The difference in analgesia can probably be explained by their study design; that is, they used a large bolus epidural dose and an epidural test dose that included lidocaine and epinephrine, both of which could increase spinal selectivity in analgesia by mechanisms described before. In a previous laboratory study, we also found that elevation of the end-tidal carbon dioxide level and a reduction in the ventilatory response to inspired carbon dioxide were seen together after an epidural bolus dose of 1,000 μg (similar to the dose used by Penon et al.), but the duration was relatively short. Although the total epidural dose of alfentanil in the current study was similar to those used in these two earlier reports, infusion during a 2-h period limited the peak plasma alfentanil concentrations and resultant delivery, through the systemic circulation, to the brain stem. Finally, it may be possible that even the small amount of epinephrine used in the test doses of earlier studies could have favored...
spinal redistribution and rostral spread of alfentanil in the cerebrospinal fluid to the brain stem.

Several clinical investigations have compared epidural and intravenous alfentanil in patients after operation. In an early study, Chauvin et al.55 found very similar plasma concentration-time profiles but significantly greater analgesia with epidural administration. However, the fact that patients were not blinded may have biased study findings. In addition, it is not known whether patients in the epidural group received local anesthetic or epinephrine before alfentanil. In another unblinded study, Camu and Debuquoy5 reported a slower onset and lower plasma alfentanil concentrations during the first hour with epidural administration. Thereafter, analgesia and plasma concentrations were identical. However, conclusions about analgesic mechanisms are tenuous because the infusion doses were relatively large and may have obscured potential differences between the two routes. Chauvin et al.56 also compared intravenous and epidural alfentanil in a double-blinded study using patient-controlled analgesia to titrate the dosage to the minimum necessary. Patients reported equivalent analgesia and side effects and used less drug with epidural administration. However, conclusions cannot be made about mechanisms without measurements of the plasma alfentanil concentration.

Finally, our findings are consistent with those of a recent double-blinded clinical investigation using a similar infusion dose of alfentanil. In that study, van den Nieuwenhuyzen et al.56 compared epidural and intravenous alfentanil combined with epidural bupivacaine in patients undergoing major pelvic surgery. All patients received epidural bupivacaine, 0.125%, in an infusion of 8 ml/h, and epidural or intravenous alfentanil in an infusion of 560 µg/h for 24 h. Inadequate analgesia was treated with intravenous patient-controlled morphine. Plasma alfentanil concentrations were similar to those we measured in our study. No differences in analgesia, side effects, epidural block, supplemental morphine use, or plasma alfentanil concentrations were seen. Thus, neither a spinal analgesic mechanism nor a clinical advantage was demonstrated by the epidural route, despite the inclusion of local anesthetic. It is possible that the inclusion of local anesthetic may have overwhelmed and thus obscured potential differences between the modes of alfentanil delivery, but if this were true, the differences and any potential clinical advantages are likely to be quite small.

One possible source of bias in our study was the effect of treatment order. Although the participants were blinded to treatment order, the study design necessitated that the epidural infusion always preceded the intravenous administration. However, this effect was at least partially controlled by the inclusion of a placebo day, the timing of which was counterbalanced so an equal proportion of participants received placebo infusions on the first, second, and third epidural study days.

We compared the effects of epidural and intravenous alfentanil infusions in healthy volunteers. We found that epidural alfentanil produced analgesia that was no greater than intravenous alfentanil when plasma opioid concentration time courses were matched. We observed clear, selective, lower-extremity analgesia in only two of volunteers after they received epidural alfentanil. Side effects were also similar for both routes of administration. Thus, systemic absorption and a supraspinal mechanism appear to explain most of the analgesia seen with an epidural bolus dose of 400 µg followed by a 400-µg/h infusion of alfentanil. Regardless of the mechanism, our findings support other clinical investigators’ conclusions that epidural administration of alfentanil does not offer a clear clinical advantage compared with the intravenous route.

The authors thank Dr. Barry Storer for assistance with the statistical analysis and Dr. Christopher Bernards for his helpful discussion.

References

8. Chrubasik J, Chrubasik S, Ren Y, Schulte-Monting J, Martin E:

Anesthesiology, V 90, No 1, Jan 1999
Epidural versus subcutaneous administration of alfentanil for the management of postoperative pain. Anesthesiology 1994; 78:1141-8


33. Bernard CM, Hill HF. Morphine and alfentanil permeability through the spinal dura, arachnoid, and pia mater of dogs and monkeys. Anesthesiology 1990; 73:1214-9

34. Bernard CM, Hill HF. Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. Anesthesiology 1993; 77:750-6

35. Bernard CM, Sorkin LS. Radicular artery blood flow does not redistribute fentanyl from the epidural space to the spinal cord. Anesthesiology 1994; 80:872-8


46. van den Nieuwenhuyzen MO, Stienstra R, Barm AGJ, Vletter AA, van Kleef JW. Efficacy of alfentanil as an adjuvant to epidural bupivacaine in the management of postoperative pain following laparotomies (abstract). Anesthesiology 1997; 87:A794