# More Epidural than Intravenous Sufentanil is Required to Provide Comparable Postoperative Pain Relief

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The extent to which epidurally administered sufentanil acts directly on spinal opioid receptors remains controversial. We tested the hypothesis that small-dose boluses of sufentanil, given epidurally or IV, provide comparable analgesia at similar plasma sufentanil concentrations. The lipophilicity of sufentanil makes it likely to be absorbed into fat surrounding the epidural space. We therefore also tested the hypothesis that more epidural than IV sufentanil is required to produce comparable analgesia. Analgesia and plasma sufentanil concentrations were evaluated in 20 postoperative patients randomly assigned to patient-controlled epidural or IV sufentanil. Pain was evaluated with visual analog scales by blinded observers. Sufentanil doses and plasma concentrations were measured. Analgesia was similar with epidural and IV sufentanil administration. Plasma sufentanil concentrations were virtually identical in the two groups. However, significantly larger sufentanil doses were required with epidural administration: 238 ± 50 μg vs 160 ± 32 μg ($P < 0.01$). The primary mechanism by which small-dose boluses of epidurally-administered sufentanil produce analgesia seems to be systemic absorption of the drug with subsequent recirculation to the supraspinal opioid receptors. This study demonstrates that the cumulative dose of sufentanil, when administered as a small epidural bolus, is approximately 50% more than that administered IV to provide comparable analgesia. This indicates that the bioavailability of epidurally-administered sufentanil is reduced and suggests that a large proportion of the drug may be absorbed into the epidural fat.

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The lipophilic opioid sufentanil is often used for postoperative epidural analgesia (1). The theory supporting epidural administration of sufentanil is that the drug acts on opioid receptors in the dorsal horn of the spinal cord, thus providing analgesia in the affected dermatomes with fewer supraspinal side effects. However, the extent to which epidurally administered sufentanil acts directly on spinal opioid receptors remains controversial (1).

The size of the dose seems to be a critical factor. When given in boluses exceeding 10 μg, sufentanil has a preferential spinal effect (2–6). In contrast, analgesia with continuous infusions of small-dose sufentanil is primarily mediated by systemic absorption of the drug, with subsequent recirculation to supraspinal centers (7–10). Epidural patient-controlled analgesia (PCA) allows patients to titrate small boluses of analgesic to their needs. The doses of sufentanil given with this method are generally <5 μg (11). Patient-controlled epidural administration of sufentanil may thus offer little advantage over IV administration. The primary objective of this study was therefore to test the hypothesis that at similar analgesic levels, plasma sufentanil concentrations are similar with epidural and IV administration.

Sufentanil is better absorbed from the epidural space than is morphine because it is far more fat soluble. Its lipophilicity also makes it likely to be absorbed into the fat surrounding the epidural space. Our secondary objective was therefore to test the hypothesis that more epidural than IV sufentanil is required to produce comparable analgesia.

## Methods

After informed consent and institutional approval, 20 patients scheduled to undergo major abdominal or

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urologic procedures with general anesthesia were enrolled in the study. All were between 18 and 65 yr old, and all were ASA physical status I or II. Exclusion criteria included a history of chronic pain, routine analgesic use, drug or alcohol abuse, chronic inflammatory disease (including inflammatory bowel disease), psychiatric disorders, or contraindications to the self-administration of opioids (i.e., inability to understand the PCA device).

No premedication was given. On the evening before surgery, patients were instructed in the use of a 10-cm-long visual analog scale (VAS; 0 = no pain to 10 = worst possible pain) and the PCA device.

An epidural catheter was inserted before surgery via the T8-9 or T9-10 interspace by using standard procedure. Correct catheter position was confirmed by a test dose of 4 mL of 1.5% lidocaine with 1:200,000 epinephrine. Anesthesia was induced with thiopental, fentanyl, and vecuronium and maintained with isoflurane in nitrous oxide and oxygen. At the end of the surgical procedure, residual neuromuscular block was antagonized with atropine and neostigmine. When spontaneous ventilation was reestablished, the patients' tracheas were extubated.

In the postanesthesia care unit, the patients were randomly allocated to double-blinded administration of IV ($n$ = 10) or epidural ($n$ = 10) sufentanil. Randomization was based on computer-generated codes that were maintained in sequentially numbered opaque envelopes until just before use. Patients were fully informed before the operation that they would be given placebo through the epidural catheter during the study period if they were allocated to the IV group.

When patients were sufficiently alert and complained of pain (VAS >5 cm), those in the Epidural group were given an epidural bolus of 15 $\mu$g of sufentanil, whereas those in the IV group were given epidural saline. A PCA pump (3300 PCAS; Graseby, Watford, UK), loaded with sufentanil diluted to 5 $\mu$g/mL, was connected to both the IV catheter and the epidural catheter by way of a hidden three-way stopcock. The stopcock was positioned according to the randomization assignments. The PCA device was set to deliver sufentanil as a 1-mL bolus, followed by a 5-min lockout interval, with no background infusion or limits. PCA was maintained for 24 h.

Venous blood was sampled for sufentanil analysis before sufentanil administration, 1 h after sufentanil administration, and at 4-h intervals for 24 h starting 4 h after sufentanil administration. Blood was centrifuged and stored at −40°C until analyzed.

Patients were not told to which group they had been assigned; all investigators involved in evaluating analgesia and other subjective responses were blinded to the patients' group assignments. Pain scores were recorded before the epidural sufentanil or saline bolus and then after 10 min, 20 min, 1 h, and 2 h. Pain was subsequently evaluated at 2-h intervals for a total of 24 h.

Sedation was monitored at the same intervals by using the following four-point rating scale: 0 = patient fully awake, 1 = patient somnolent and responsive to verbal command, 2 = patient somnolent and responsive to tactile stimulation, and 3 = patient asleep and responsive to painful stimulation. Respiratory depression was defined as persistent sedation, a respiratory rate of <10 breaths/min, and hypoxemia with oxygen saturation ($Spo_2$) <90%. Side effects such as nausea, vomiting, pruritus, dysphoria, and diplopia were noted.

Sufentanil plasma concentrations were determined in duplicate by radioimmunoassay. An assay volume of 1 mL, previously adjusted to pH 10, was extracted on an Extrelut 3 (Merck, Darmstadt, Germany) column with a heptane-isoamyl alcohol mixture (98.5:1.5) as the elution solvent. The solvent was evaporated to dryness, and the extract was dissolved in a small volume of distilled water containing 10% blank plasma. This solution was evaluated by radioimmunoassay. The lower limit of sensitivity was 50 pg sufentanil per milliliter of plasma; interassay coefficients of variation and accuracy, based on quality control samples, were 12.0% and 99.1%, respectively (12).

IV sufentanil consumption was used to calculate the statistical power. According to a previous study (7), we anticipated the mean IV PCA sufentanil use over 24 h to be 200 $\mu$g with an SD of 40 $\mu$g. A sample size estimate indicated that eight patients per group would give a power of 80% at an $\alpha$ level of 0.05 for detecting a difference of at least 30% in sufentanil consumption between the two groups. The study was thus prospectively set to 20 patients, with 10 assigned to each treatment group.

Plasma sufentanil concentrations were integrated over the period from 0 to 24 h after the epidural bolus by using the trapezoidal rule (13). Statistical analyses were performed with NCSS 6.0 (Statistical Solution, Cork, Ireland). Continuous variables were compared by using unpaired, two-tailed $t$-tests or one-way analysis of variance. The relative frequencies of sex, surgical procedures, and side effects in the groups were compared by using Fisher's exact tests. Sedation scores were compared by using Mann-Whitney $U$-tests. Results are presented as mean ± SD or median and 25%–75% interquartile ranges; $P < 0.05$ was considered statistically significant.

## Results

Ten patients were enrolled in each group and completed the study. Demographic data, the type and

length of the surgical procedures, and intraoperative fentanyl dose were comparable in the Epidural and IV groups (Table 1). The interval between the end of surgery and the epidural bolus was similar in the Epidural (2.3 ± 1.8 h) and IV (2.5 ± 1.6 h) groups.

The two groups also had comparable sedation scores (median, 1; 25%–75% interquartile range, 1–2 in the two groups during the study period). The incidence of nausea and vomiting requiring treatment was also similar: four in the Epidural and three in the IV group. No patient in either group reported dysphoria, hallucinations, pruritus, or diplopia. Although there were no reports of clinical respiratory depression, as defined in Methods, during the study, five patients in the Epidural group and six patients in the IV group developed an $Spo_2$ <90% and were treated with oxygen.

Pain, as assessed by the VAS, did not differ significantly in the two groups (Fig. 1). However, cumulative sufentanil consumption, including the initial epidural bolus, was 49% more in the Epidural group (238 ± 50 μg vs 160 ± 32 μg, $P < 0.01$, Fig. 2).

Plasma concentrations of sufentanil were comparable in the two groups (Fig. 3). Integrated sufentanil concentrations were also similar: 2.2 ± 0.9 $ng \cdot mL^{-1} \cdot h^{-1}$ in the Epidural group and 2.6 ± 1.3 $ng \cdot mL^{-1} \cdot h^{-1}$ in the IV group.

## Discussion

Epidurally administered opioids can provide analgesia via three mechanisms: stimulating opioid receptors in the spinal cord, transport to supraspinal and spinal receptors by cerebrospinal fluid, or blood-borne transport to supraspinal receptors after systemic absorption. Our study evaluated the contribution of systemic absorption by comparing blood concentrations and analgesia after IV and epidural administration of sufentanil.

After one hour, plasma concentrations of sufentanil were virtually identical, roughly 0.1 ng/mL, after each route of administration. These concentrations were well within the range of effective concentrations (0.01–0.56 ng/mL) reported after major gynecologic surgery with PCA (14). Plasma concentrations of sufentanil in a similar range have also been reported with epidural administration (15).

Not only were plasma concentrations similar during epidural and IV sufentanil administration, but analgesia was also virtually identical. Patients in both groups experienced considerable pain immediately before the start of PCA; however, pain scores in each group decreased to ≈4 cm within an hour and averaged only ≈3 cm after 10 hours. Furthermore, sedation scores were comparable in the two groups, as were other opioid-related complications such as nausea, pruritus, and desaturation.

**Table 1.** Patient Characteristics and Intraoperative Data

| Variable | IV | Epidural |
|---|---|---|
| Age (yr) | 51 ± 7 | 53 ± 10 |
| Sex (M/F) | 6/4 | 6/4 |
| Weight (kg) | 67 ± 8 | 68 ± 9 |
| Height (cm) | 168 ± 6 | 169 ± 9 |
| Procedure (No. patients) | | |
| Gastrectomy | 2 | 2 |
| Colectomy | 5 | 6 |
| Nephrectomy | 3 | 2 |
| Length of surgery (h) | 3.2 ± 1.2 | 3.1 ± 1.5 |
| Intraoperative fentanyl (μg) | 380 ± 140 | 350 ± 180 |

Data are presented as mean ± SD unless otherwise noted.

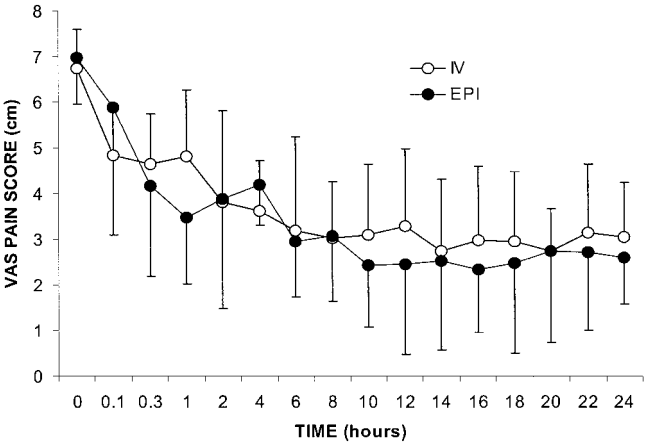


**Figure 1.** Visual analog scale (VAS) pain scores in the Epidural (EPI) and IV groups during the 24-h period after the start of patient-controlled analgesia. Data are presented as mean ± SD.

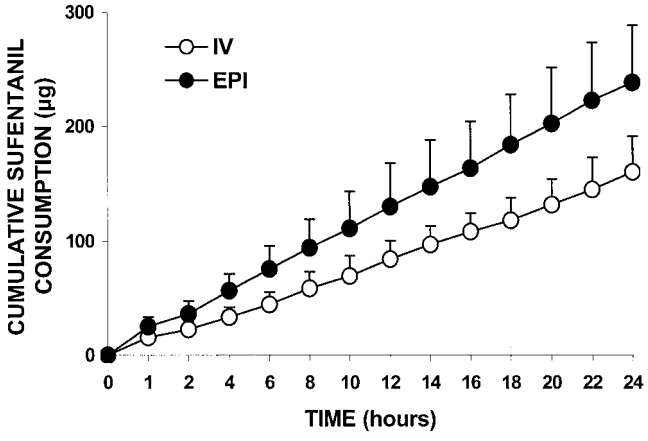


**Figure 2.** Cumulative sufentanil consumption in the Epidural (EPI) and IV groups during the 24-h period after the start of patient-controlled analgesia. Epidural sufentanil consumption includes the initial loading dose of 15 μg. Area under the curve differed significantly for the two groups ($P < 0.01$). Data are presented as mean ± SD.

Plasma sufentanil concentrations, pain relief, and opioid-induced complications were all comparable in each group. These data support the belief that the primary mechanism by which epidurally administered

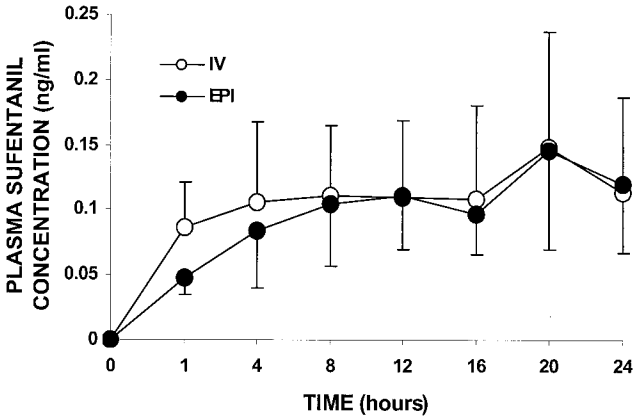


**Figure 3.** Plasma sufentanil concentration in the Epidural (EPI) and IV groups during the 24-h period after the start of patient-controlled analgesia. Data are expressed as mean ± SD.

sufentanil produces analgesia is via systemic absorption of the drug with subsequent recirculation to supraspinal opioid receptors. However, in this study, we did not study larger bolus doses of epidural sufentanil, and we did not investigate other supraspinal effects, such as ventilatory responses to $CO_2$ and pupillary constriction. Indeed, our results are likely attributed to the fact that we studied the effects of small-dose boluses. Larger bolus doses probably exert their effects through a combination of spinal and supraspinal actions (2,4,5), suggesting that the extent of concentration gradient is determinant to facilitate the lipid-soluble transfer from the epidural space, through the meninges, and into the spinal cord.

Although plasma concentrations were similar, patients assigned to epidural opioid required nearly 50% more sufentanil to achieve comparable pain relief; this demonstrated that the systemic bioavailability of sufentanil administered epidurally was <1 during the study period. Although venous plasma concentrations may not reflect effect site concentrations, we did not measure the cerebrospinal fluid sufentanil concentrations for ethical reasons. Our results nonetheless suggest that sufentanil was absorbed into epidural fat, and this is consistent with its extreme lipophilicity. This theory is also consistent with a postmortem study in which sufentanil concentrations in epidural fat and the spinal cord were measured after chronic epidural infusion. The largest sufentanil concentrations were found in epidural fat near the tip of the catheter (16). Moreover, the progressive and divergent increase in the cumulative sufentanil doses that we observed suggested that the epidural fat was not saturated during the study period.

Our result that more epidural than IV sufentanil is required is consistent with previous studies that reported a loss of apparent narcotic epidural potency as lipophilicity increased. An animal study, for example, demonstrated that the subcutaneous/epidural 50% effective concentration ratio producing analgesia was smaller with sufentanil than with fentanyl (17). Similarly, the IV/epidural analgesic dose ratio for sufentanil was less than that for fentanyl (18). In contrast, similar doses of epidural and IV fentanyl are required to produce comparable analgesia (19). Moreover, comparable analgesia with epidural alfentanil (20), meperidine (21), or hydromorphone (22) is achieved with 50%–75% of the IV dose. In contrast, only 10%–20% as much morphine is required epidurally as IV (21). The pattern here is clear: relative epidural potency is inversely related to lipid solubility (17). Thus, relatively water-soluble opioids, such as morphine, are far more effective when given epidurally than IV. In contrast, highly lipophilic drugs, such as fentanyl, offer no benefit. Our results extend this pattern by demonstrating that the most lipophilic clinically available opioid, sufentanil, is considerably less effective when given epidurally than IV.

Our findings contrast with two studies in which PCA administration of sufentanil produced comparable analgesic potency when given IV or epidurally (3,7). However, their protocols differed significantly from ours. In one, patients were given epidural local anesthetic and epinephrine before sufentanil (3). In the other, a continuous infusion of sufentanil was combined with PCA boluses; this may have obscured potential differences between the two delivery modes (7). Our study is thus the first to compare analgesia and plasma pharmacokinetics of PCA IV and epidural sufentanil with small-dose boluses without a background infusion or prior use of local anesthetics.

Small doses of lipophilic opioids are often administered epidurally as adjuncts to local anesthetics to provide analgesia during labor or in the postoperative period. A epidural PCA syringe containing these two compounds may be proposed. However, our study highlights questions concerning the reality of the primary spinal interaction between small doses of epidural sufentanil and local anesthetics. As yet, no study has compared the efficacy of epidural versus IV administration of sufentanil with an epidural local anesthetic for acute pain relief. Two recent studies (23,24) using this protocol design were published regarding fentanyl used during labor and concluded that small epidural doses of fentanyl exert a local anesthetic-sparing activity and an increased dermatomal level, primarily via a spinal site of action rather than a supraspinal effect. However, these studies were performed for a short time, and it is possible that over time, as more fentanyl is administered, supraspinal analgesia may predominate over spinal effects. In agreement with this hypothesis, Van den Nieuwenhuyzen et al. (25) found that, when combined with small-dose bupivacaine over 24 hours, IV alfentanil

was as effective as epidural alfentanil for the management of postoperative pain. These data suggest that after a few hours, the systemic action of alfentanil predominates. Further support for this theory is provided by the gradually increasing sufentanil plasma concentrations that we observed in the Epidural group during the first four to eight hours.

In conclusion, epidural and IV sufentanil administered as small-dose boluses via a PCA device resulted in virtually identical plasma sufentanil concentrations and comparable postoperative analgesia and opioid-related side effects. Furthermore, sufentanil dose requirements were about 50% larger when given epidurally. These findings emphasize the prominent supraspinal mechanism via systemic absorption of epidural small-dose sufentanil and are consistent with previous studies indicating that the relative efficacy of epidural opioids is inversely related to their lipophilicity. Our results, though, suggest that a given dose of sufentanil is less effective when given epidurally than when given IV.

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