

A Prospective, Randomized, Double-blind Comparison of Epidural and Intravenous Sufentanil Infusions

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Background: The site of action (spinal vs. central) of epidurally administered lipid-soluble opioids has been the subject of controversy. We compared the efficacy, plasma concentration and side effects of epidural and intravenously administered sufentanil for postoperative pain relief.

Methods: Using a double-blind, prospective design, 50 patients scheduled for intraabdominal operations during combined epidural-general anesthesia were randomized into one of two groups. Patients in group 1 ($n = 24$) received a 1- $\mu\text{g}/\text{ml}$ sufentanil infusion epidurally at $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and a saline infusion intravenously at the same rate. Patients in group 2 ($n = 26$) received a 1- $\mu\text{g}/\text{ml}$ sufentanil infusion intravenously at $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and a saline infusion epidurally at the same rate. Intravenous morphine sulfate was available in 2-mg increments to all patients in the postanesthesia care unit until visual analogue scale (0-100 mm) pain score was ≤ 30 . Then, a patient-controlled intravenous pump providing morphine on demand (1 mg with a 10-min lockout) was begun. Blood samples were drawn for sufentanil plasma levels and patients were assessed for pain, sedation and nausea for the 48 h after commencement of the infusions.

Results: Similar visual analogue pain, sedation, and nausea scores were found between the patients in the two groups. No differences were found in supplemental morphine requirements and plasma sufentanil concentrations between the patients in the two groups. A higher incidence of excessive se-

dation requiring infusion decrease was found in the intravenous group (six vs. one, $P < 0.05$).

Conclusions: Many clinical similarities were found when epidural and intravenous sufentanil infusions were compared. The higher incidence of excessive sedation in the patients receiving intravenous sufentanil could not be explained on the basis of plasma sufentanil concentrations alone. This study indicates that little clinical difference exists between epidural and intravenous administration of sufentanil. (Key words: Analgesia: postoperative. Analgesics, epidural: sufentanil. Analgesics, intravenous: sufentanil. Anesthetic techniques: epidural.)

OPIOIDS administered into the epidural space are widely used for the control of postoperative pain.^{1,2} Water-soluble opioids (e.g., morphine) have been shown to exert their effect primarily at the dorsal horn ganglia of the dorsal spinothalamic tract,³ but the site of action of lipid-soluble opioids (e.g., fentanyl, alfentanil, and sufentanil) is less clear. Some investigators⁴⁻⁶ have indicated that the effects of opioids with lipid solubility greater than that of morphine are similar with either epidural or intravenous administration. They postulate that the analgesic effect seen by both intravenous and epidural routes is probably a systemic effect produced by binding to central periventricular μ -opioid receptors. Not all researchers agree, however, citing significant clinical differences between epidural and intravenous administration of lipid-soluble opioids.⁷⁻⁹ We undertook this study to compare the efficacy, plasma levels, and side effects of sufentanil when administered epidurally and intravenously at equivalent doses and volumes.

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 25A.

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Materials and Methods

The study was conducted in a double-blind, prospective, and randomized fashion. The study protocol was approved by the Institutional Review Board and all patients gave their informed, written consent to

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participate in the study. Patients were considered candidates for participation in the study if they were scheduled for intraabdominal operations during combined epidural–general anesthesia. Exclusion criteria included contraindications to placement of an epidural catheter (*e.g.*, coagulopathy, local infection, or septicemia), opioid use during the 2 weeks before the procedure, pregnancy, inability to use the patient-controlled analgesia device or allergy to any of the study medications.

No patient received sedative or opioid premedication. Before induction of anesthesia, each patient had an epidural catheter (Peri-fix, Burrion, Bethlehem, PA) placed in the lumbar region and threaded 3–5 cm into the epidural space. Ten to 20 ml of 2% lidocaine with 1:200,000 epinephrine (Xylocaine, Astra Laboratories, Westborough, MA) was administered through the catheter. An appropriate dermatomal anesthetic sensory level was documented before the induction of general anesthesia. Anesthesia was induced with intravenous propofol 1–2 mg/kg. Vecuronium bromide, 0.1 mg/kg intravenously, was given to facilitate tracheal intubation. No opioids were given as part of the intraoperative anesthetic technique. After induction of general anesthesia, patients had anesthesia maintained with a 70:30 N₂O–O₂ mixture or as necessary to maintain hemoglobin O₂ saturation greater than 90%. Volatile agents (*e.g.*, isoflurane or enflurane) were used as deemed necessary by the attending anesthesiologist to maintain hemodynamic stability. The administered volatile agent concentration did not exceed 1 MAC in any study patient.

If the patient did not have an intraarterial catheter, a peripheral intravenous heparin lock was placed on the contralateral arm of the study infusion for plasma sampling, postoperatively.

On initiation of wound closure, two infusions were started. Sufentanil was mixed by a research pharmacist and labeled in a blinded fashion. Sufentanil was diluted to 1 µg/ml and was infused at 0.2 µg · kg⁻¹ · h⁻¹ (= 0.2 ml · kg⁻¹ · h⁻¹). Patients were assigned randomly to one of two groups. The patients in group 1 received an epidural sufentanil infusion and a saline infusion intravenously, at the same rate. The patients in group 2 received an epidural saline infusion and sufentanil intravenously. The infusions were continued for 48 h.

If patients complained of pain in the postanesthesia care unit, 2 mg morphine sulfate, in intravenous aliquots, was administered as needed. Upon achieving patient comfort (visual analogue scale [VAS] ≤ 30), demand-only intravenous morphine sulfate with a patient-controlled analgesia device programmed to deliver 1 mg with a 10-min lockout was begun for all patients. No maintenance infusion of morphine was administered.

Patients were instructed on the use of the VAS (0–100 mm) preoperatively. On arrival to the postanesthesia care unit each patient was interviewed by a research associate who was not a member of the anesthetizing team (*i.e.*, approximately 30 min after study infusion commencement), 1 h after arrival in the postanesthesia care unit, every 8 h for 24 h and at 36 and 48 h after infusion commencement. Separate VAS scores were obtained for pain at rest and while coughing, for nausea, and for sedation. Patients also were queried regarding pruritus and urinary retention.

The amount of morphine required for patient comfort in the postanesthesia care unit was measured in all patients. The amount of morphine required to maintain satisfactory analgesia throughout the 48 h was measured and recorded. If the patient reported inadequate pain relief (VAS ≥ 70), the following procedure was implemented. The patient was reeducated on the use of the intravenous patient-controlled analgesia device for pain relief. If this was insufficient to control pain, or if the patient had used the machine appropriately, the intravenous morphine demand dose was increased to 2 mg with the same 10-min lockout interval.

Excessive sedation (sedation VAS ≥ 70) or respiratory depression (respiratory rate < 8 breaths/min) were treated as follows. If either excessive sedation or respiratory depression occurred, both infusions (intravenous and epidural) were stopped for 30 min and restarted at one half the initial rate.

Blood samples for sufentanil assay were drawn at 1, 8, 16, 24, 36, and 48 h after infusion commencement. The samples were centrifuged and frozen within 30 min of sampling. Plasma sufentanil concentrations were determined by radioimmunoassay. § The interassay coefficient of variation for the sufentanil assay averaged 10.73% over 0.10–8.0 ng sufentanil/ml plasma. Replicate analyses of control plasma samples, covering the therapeutic range of concentrations, yielded relative errors of less than 10% for each concentration. The lower limit of sensitivity was 0.05 ng sufentanil/ml plasma.

§ The assays were performed at the analytic laboratory of Dr. Steven Bai at North Carolina State University.

This study was designed to test the null hypothesis that there were no differences in analgesia, opioid requirement, or side-effects in patients who received epidural *versus* intravenous sufentanil during the first 48 h after surgery. The two-factor analysis of variance was used to test the null hypothesis. In this case, the two-factor analysis of variance included pooling of data to determine whether or not there was a *group effect* (*i.e.*, ignoring data collection intervals), a *time effect* (*i.e.*, ignoring groups), and an *interaction between group·time factors* for each continuous response variable. The two-factor analysis of variance was used to analyze differences in VAS scores for pain, sedation, and nausea, morphine sulfate requirement, respiratory rate, and plasma concentrations of sufentanil. When $P \leq 0.05$, Scheffé's multiple-comparisons test was used to distinguish differences in measurement variables obtained at data collection intervals. Intergroup categorical data (*e.g.*, gender distribution, requirement for decrease in sufentanil infusion, or incidence of pruritus) were compared with a chi-squared test. Spearman's correlation was used to statistically evaluate the association between plasma sufentanil concentration and VAS pain and sedation scores. Differences were considered statistically significant if $P \leq 0.05$.

Results

Fifty patients were studied, 24 in group 1 and 26 in group 2. There were no differences between the groups with respect to age, weight, gender, or ASA classification (table 1). A list of the operations performed on the study patients is included in table 2.

The results of the VAS pain scores are reported in figure 1. No differences were found between the patients in the two groups with respect to their level of pain, either at rest or while coughing.

The amount of supplemental morphine required to attain satisfactory analgesia was similar between the

Table 2. Operative Procedures Performed

Epidural (n = 24)	Intravenous (n = 26)
Radical prostatectomy (5)	Exploratory laparotomy (10)
Radical cystectomy (5)	Radical nephrectomy (4)
Radical hysterectomy (4)	Radical prostatectomy (3)
Exploratory laparotomy (3)	Radical cystectomy (2)
Colectomy	Gastrectomy (2)
Esophagogastrectomy	Colectomy
Gastrectomy	Florida pouch
Nephrectomy	Hepatic lobectomy
Pelvic exenteration	Pelvic exenteration
Retroperitoneal exploration	Radical hysterectomy
Whipple's procedure	

Values in parentheses represent numbers of specific procedures performed.

patients in the two groups (fig. 2). Statistically significant differences between the patients in the two groups was found only at 36 h.

The patients in the two groups demonstrated different sedation scores at only one assessment point (fig. 3). There was a significant difference in the number of patients requiring adjustment of the sufentanil infusion rate because of excessive sedation or respiratory depression (table 3). Six patients in group 2 required discontinuation and adjustment of their infusion at a lower dose, whereas only one patient in group 1 required infusion rate adjustment ($P < 0.05$). No patient developed respiratory depression.

The nausea scores are depicted in figure 4 and were similar in the patients in the two groups. There were no differences between the patients in the two groups with respect to the incidence or severity of pruritus. Urinary retention could not be effectively evaluated, as the majority of patients in both groups had indwelling urinary catheters.

No differences were found between the patients in the two groups with respect to plasma sufentanil concentrations at any time during the study period (fig. 5).

Discussion

This study compared epidural and intravenous sufentanil in an attempt to find clinically significant differences between the two routes of administration. Some investigators have not observed differences when these two routes of drug delivery are compared for lipid-soluble opiates⁴⁻⁶; yet not all agree in this regard.⁷⁻⁹

Table 1. Demographic Characteristics of the Study Groups

	Epidural (n = 24)	Intravenous (n = 26)
Age (yr)	62 ± 16	64 ± 14
Weight (kg)	81 ± 18	75 ± 20
Gender (male/female)	16/8	11/15
ASA physical status (range 1-3)	2	2

Values are expressed as mean ± SD except gender (which is reported as incidence) and ASA physical status (which is a median).

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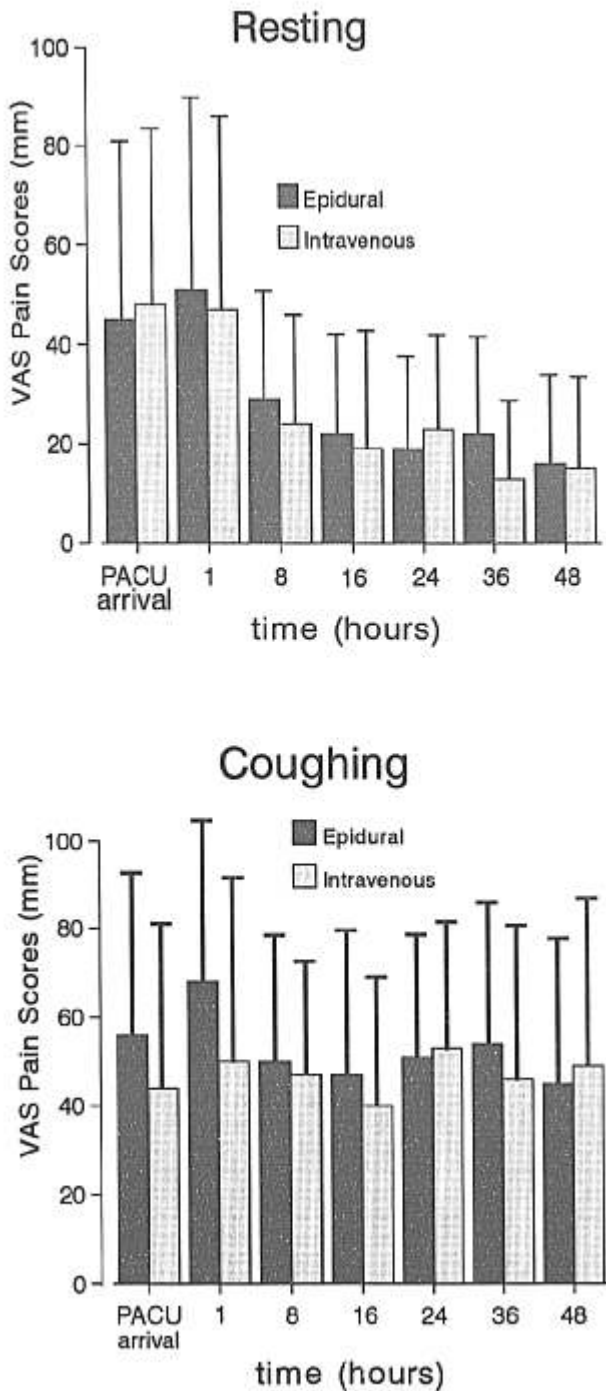


Fig. 1. Pain VAS scores (0–100 mm) reported at rest and while coughing by the patients in the two groups. Values are expressed as mean ± SD. The differences between the patients in the groups were not statistically significant.

Some of the studies which show no differences have methodologic flaws which may prevent the development of definitive conclusions based on their results. Ellis *et al.*⁵ compared intravenous to epidurally administered fentanyl in 28 patients (12 in the intravenous and 16 in the epidural group) and found that fentanyl given intravenously was inadequate to control pain at the maximum allowable dose of $2.25 \mu \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in three patients. These patients were excluded from statistical analysis. Including these patients with inadequate pain relief after intravenous fentanyl could have changed their results. The methodology used in their study did not allow them to increase the intravenous infusion of fentanyl. Increasing the amount of fentanyl administered in these patients could have raised intravenous fentanyl requirements into the statistically significant range compared with epidural fentanyl requirements. Pain VAS scores were not different between the groups in their study, which is not surprising, because the infusion rate was titrated to patient comfort.

We also found no difference in pain relief in the patients in our study, however, we do not feel that this is a significant point. Patients who receive pain medication in a patient-controlled manner should be able to autotitrate their medication to achieve adequate re-

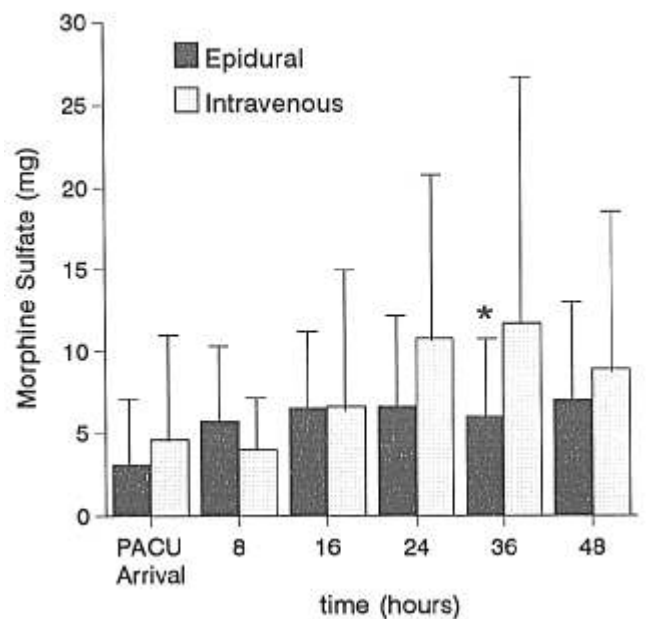


Fig. 2. Supplemental intravenous morphine requirements of the patients in the two groups. Values are expressed as mean milligrams ± SD. * $P \leq 0.05$.

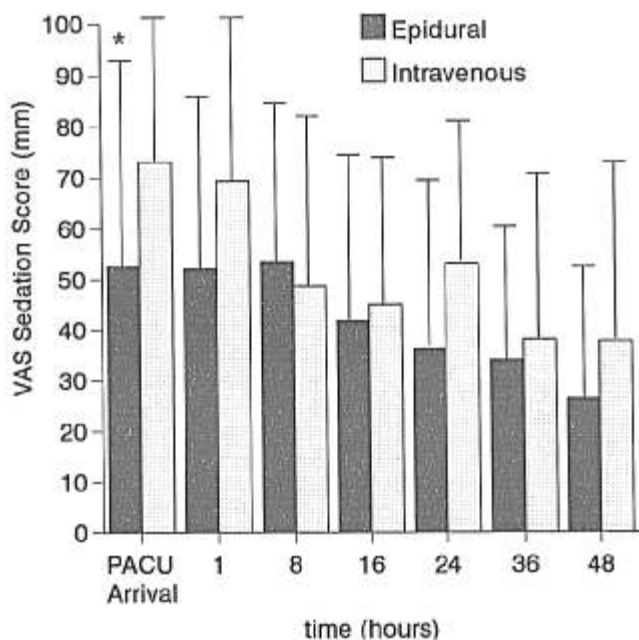


Fig. 3. Sedation VAS scores (0-100 mm) reported by the patients in the two groups. Values are expressed as mean ± SD. *P ≤ 0.05.

lief. This may account for the similarities in pain relief found in other studies when these two routes are compared and autotitration of supplemental pain medication is available to the patient.⁴⁻¹⁰ A more objective factor in delineating the differences between epidural and intravenous administration under these circumstances may be the amount of opioid required to attain acceptable pain relief. Several groups of investigators have found a significant reduction in fentanyl requirements when using the epidural route compared with intravenous administration.^{7-9,11} We used a continuous infusion of sufentanil by both routes and measured supplemental intravenous morphine requirements as an indicator of an opioid-sparing effect. Although a 25% reduction in mean total supplemental morphine requirements (34 ± 18 mg/48 h vs. 46 ± 44 mg/48 h) for maintenance of satisfactory analgesia was found in the patients who received epidural sufentanil, that difference did not reach statistical significance.

Excessive sedation was found more commonly in the patients receiving intravenous sufentanil. Six patients in the intravenous group demonstrated excessive sedation requiring a decrease in the sufentanil infusion rate compared with one patient in the epidural group. Although this finding did not contribute to significant

Table 3. Patients Requiring Sufentanil Infusion Decrease

Epidural (n = 24)	Intravenous (n = 26)
1*	6

* P ≤ 0.05 versus intravenous.

morbidity, persistence or worsening of excessive sedation could conceivably lead to loss of protective reflexes, hypoventilation, atelectasis and respiratory depression. Guinard *et al.*,¹⁰ in a study comparing intravenous, lumbar epidural, and thoracic epidural fentanyl after thoracotomy found similar VAS pain scores at comparable fentanyl infusion rates. However, they also found improved pulmonary function, a lower need for supplemental intravenous fentanyl and a shorter hospital stay for those patients who received thoracic epidural fentanyl. In contrast to the current study, Guinard *et al.* observed no difference between epidural and intravenous groups when considering the numbers of patients requiring a decrease in their infusion rate. As they pointed out, the absence of severe respiratory

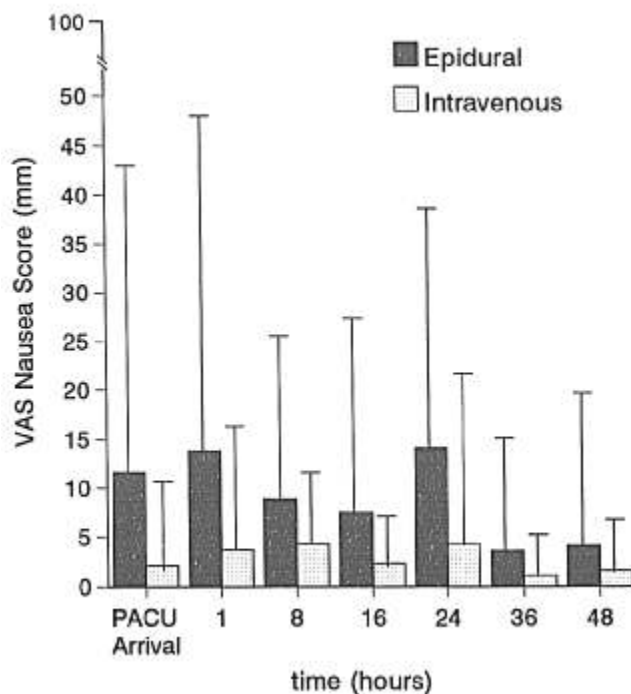


Fig. 4. Nausea VAS scores (0-100 mm) reported by the patients in the two groups. Values are expressed as mean ± SD. The differences between the patients in the groups were not statistically significant.

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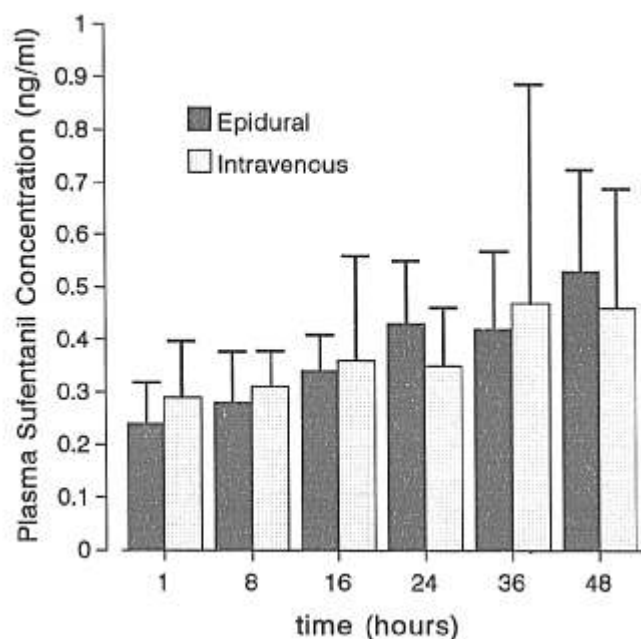


Fig. 5. Plasma sufentanil concentrations found in the patients in the two groups. Values are expressed as mean \pm SD. The differences between the patients in the groups were not statistically significant.

depression may be due to close surveillance and the resultant reduction in fentanyl administration. Similarly, patients who demonstrated excessive sedation in our study had a rapid decrease in their infusion rate, which may have prevented progression to increased ventilatory impairment. Furthermore, the definition of respiratory depression in our study (respiratory rate $<$ 8 breaths/min) was not very sensitive. The incidence of subclinical respiratory depression may have been much higher had arterial CO_2 tension or the CO_2 response curve been used to evaluate ventilation. Recently, Geller *et al.*,¹¹ found significantly higher opioid requirements in patients receiving sufentanil intravenously compared with patients receiving sufentanil epidurally. In contrast to our study, the patients receiving intravenous sufentanil in their study had significantly higher sedation scores than the patients receiving epidural sufentanil.

Nausea scores were similar in the patients in the two groups. This is consistent with some studies⁴⁻⁶ but

contrasts with others^{7,10} who found a lower incidence of nausea with epidural administration of lipid-soluble opioids when comparing them to intravenous dosing.

It should not be surprising that measured plasma sufentanil concentration did not differ between the groups in our study. The high lipid-solubility of sufentanil (octanol:water coefficient of 1,788)¹² allows for rapid and persistent systemic uptake, resulting in similar plasma concentration when equal doses are administered by epidural and intravenous routes. As only a small amount of epidurally administered opioid is required for spinal action, most of the opioid can be found in the systemic circulation in direct relation to its degree of lipophilicity. The minimum effective analgesic concentration for sufentanil after abdominal operations has not been established as it has for fentanyl,¹³ but the mean concentrations of sufentanil found in our patients was in the range found in patients with spontaneous ventilation¹² and analgesic concentrations.¹⁴ A decrease in uptake and prolongation of analgesia may be achieved by adding epinephrine to epidural sufentanil¹⁵ although rises in plasma concentration after discontinuation of the infusion have been described.¹⁵

In summary, equivalent intravenous and epidural infusions of sufentanil produced similar pain scores and plasma sufentanil concentrations. Although sedation scores were similar between the patients in the two groups, the incidence of excessive sedation was higher in patients receiving intravenous sufentanil. These findings indicate that minor clinical differences exist between epidural and intravenously administered sufentanil.

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