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Sufentanil Analgesia Following Cesarean Section: Epidural *Versus* Intravenous Administration

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Administration of epidural opioids for the relief of postoperative pain has become a common practice in the management of cesarean section patients.[1] Although morphine and other long-acting agents have been used commonly for this purpose, the risk of delayed respiratory depression from cephalad spread of the opiate in the cerebrospinal fluid remains a disadvantage for patients who are not normally intensively monitored.[1–3] Another disadvantage of epidural morphine relates to its low lipid solubility and slow onset of action. Theoretically, these drawbacks should be less

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problematic with sufentanil, a highly lipid soluble and more rapid-acting opioid analgesic. After epidural administration, sufentanil (like other lipophilic agents) is more likely to penetrate neural tissue and either remain localized there, or be cleared by absorption into the circulation.[1] The aims of this study were: 1) to determine serum levels of sufentanil following its administration intravenously or epidurally to parturients following cesarean section; and 2) to evaluate clinical efficacy and side effects of epidural and intravenous sufentanil utilizing a randomized double-blind study design.

Materials and Methods

The protocol was approved by the Medical Committee for the Protection of Human Subjects in Research, and informed consent was obtained from all participants. The study was conducted in two separate phases. Phase I was designed to determine serum sufentanil levels in a small number of patients following either epidural or intravenous (iv) administration of sufentanil for post-cesarean analgesia. Phase II was designed to evaluate the clinical efficacy and side effects of intravenous and epidural sufentanil administered in a randomized double-blind manner. In both phases of the study, patients were healthy parturients undergoing elective cesarean section at term. Epidural anesthesia was performed at the L_{2-3} or L_{3-4} level, with the patient in the sitting position. An epidural catheter was introduced 2–3 cm into the epidural space. Surgical anesthesia to the T_4 level was obtained with 2% lidocaine with 1:200,000 epinephrine, supplemented with 3% 2-chloroprocaine if necessary during the operation. Patients received no narcotic analgesics prior to administration of the study drug.

Phase I. Ten minutes following delivery of the infant, patients received either: iv sufentanil, 30 μg (n = 6); epidural sufentanil, 30 μg (n = 6); epidural sufentanil, 50 μg (n = 6); or epidural sufentanil, 50 μg, with epinephrine 1:200,000 (n = 5). The intravenous injection was administered over a 3–5 min period. Venous blood was obtained from a large antecubital vein *via* a 16-gauge intravenous catheter connected to two three-way stopcocks; 5–10 ml of blood were aspirated and discarded immediately prior to obtaining each blood sample (which was stored in a red-top vacutainer tube). Venous blood samples were obtained at 5–15-min intervals for the first 90 min, and subsequently every 30–60 min for up to 4 h after injection. The blood specimens were centrifuged in a cold room, and the serum obtained was immediately frozen at −20° C. Serum sufentanil levels were measured using a standard radioimmunoassay technique,[4] with a lower limit of sensitivity of 0.1 ng/ml. The variability of the assay was ±12%. The duration of analgesia was reported as the time from sufentanil injection until the patient first requested additional analgesic medication. Data also were collected regarding the incidence of side effects (*e.g.*, nausea, vomiting, and pruritus). Hypotension was defined as a 30% decrease of systolic blood pressure or a systolic blood pressure of less than 100 mmHg, and ventilatory depression was defined as a respiratory rate of less than 10 breaths per minute. Level of sedation was assessed qualitatively by one of the investigators (ST). The patient was considered sedated if she was asleep or if she responded affirmatively to the question, "Do you feel sleepy?"

Phase II. On the first complaint of pain after delivery, patients were administered in a randomized, double-blind fashion either: epidural sufentanil, 50 μg (10 ml), and iv saline (2 ml) (EPI-50 group, n = 20); or iv sufentanil, 10 μg (2 ml), and epidural saline (10 ml) (IV-10 group, n = 20). Study medications were prepared by the pharmacy in identical syringes. The doses selected were based on preliminary studies with sufentanil in cesarean section patients§ which had demonstrated a brief duration of analgesia when doses lower than 50 μg were administered epidurally, and adequate analgesia when bolus doses of 10 μg were administered intravenously. Moreover, since pronounced sedation and transient respiratory depression had resulted following injection of sufentanil, 30 μg iv, in some patients in Phase I of the study, we did not consider it safe in a double-blind study to administer a bolus dose which might result in loss of consciousness and increase the risk of pulmonary aspiration.

The degree of analgesia was assessed by asking the patient to make a mark on a 100-mm linear visual analog pain scale (VAS),[5] where one end represented no pain and the other end represented the most severe pain ever experienced by the patient. Evaluations of pain with the VAS were performed before administration of the study drug and at 15-min intervals after injection for at least 1 h. The efficacy of the initial analgesic treatment also was assessed by quantitating the amount of additional narcotic required in the first 24 h postoperatively. To circumvent the problem of nursing availability and subjective judgement, we allowed the patients to self-administer sufentanil using the Abbott Life Care® patient-controlled analgesic (PCA) device for the first 24 h. The PCA orders allowed sufentanil to be administered in 5–15 μg bolus doses, with a lockout period of 10–20 min. The total dose of sufentanil administered *via* the PCA in the first 24 h after the operation was recorded. The duration of analgesia with the

§ G. Vanden Bussche, M.D. (personal communication).

study drug was the time from its administration until the patient first used the PCA device. Sedation was evaluated at 15–30-min intervals for 2 h after study drug administration using a composite sedation analog score.[5] This sedation score was obtained by calculating the average of five 100-mm visual analog scales, the extremes of which represented: wide awake and almost asleep; energetic and tired; well coordinated and clumsy; clear headed and fuzzy; and alert and drowsy, respectively. In addition to noting the incidence of side effects, the severity of nausea, vomiting, and pruritus was graded from 0–3 (0 = absent; 1 = mild; 2 = moderate; and 3 = severe).

Data were analyzed using one-way analysis of variance (Phase I), unpaired Student's *t* test (Phase II), and Chi-square analysis with Fisher's exact test for the discrete variables. A P value of less than 0.05 was regarded as significant.

Results

Phase I. The groups did not differ statistically with respect to age, height, and weight (table 1). Serum sufentanil levels are illustrated in figure 1. Peak sufentanil levels occurred within 10 min following the 30-μg iv dose and the 30-μg epidural dose (fig. 1A). Serum sufentanil levels were lowest with the 30-μg epidural dose and were barely detectable (less than 0.1 ng/ml) after 10 min. The addition of epinephrine to 50 μg of epidural sufentanil significantly decreased the sufentanil level at 10 min, and may have contributed to an increased sufentanil level at 75 min after administration (fig. 1B).

Duration of analgesia in the groups in Phase I is shown in table 1. Epidural administration of sufentanil resulted in analgesia lasting 200 ± 37 to 258 ± 16 min (mean ± SEM), whereas intravenous administration produced analgesia lasting only 108 ± 20 min. With respect to duration of analgesia, the 30 μg iv dose was significantly different from both 50-μg epidural doses, but not from the 30-μg epidural dose. Epinephrine did not significantly prolong the analgesia obtained with 50 μg of epidural sufentanil.

TABLE 1. Phase I: Patient Characteristics and Duration of Analgesia

	Intravenous 30 μg (n = 6)	Epidural 30 μg (n = 6)	Epidural 50 μg (n = 6)	Epidural 50 μg + Epinephrine (n = 5)
Age (yr)	31 ± 3	29 ± 3	31 ± 2	32 ± 1
Height (cm)	157 ± 3	163 ± 3	163 ± 3	163 ± 3
Weight (kg)	72 ± 5	79 ± 7	91 ± 5	72 ± 7
Duration of analgesia (min)	108 ± 20*	200 ± 37	220 ± 48	258 ± 16

Values are mean ± SEM.
* $P < 0.05$ *vs.* epidural 50 μg, and epidural 50 μg + epinephrine.

The incidence of side effects is summarized in table 2. Hypotension did not occur in any patient. One patient who received sufentanil, 30 μg, iv, transiently had a respiratory rate less than 8 breaths/min, but did not require treatment with a narcotic antagonist. The small numbers of patients in each treatment group precluded statistical analysis of these data.

Phase II. The two groups in Phase II were similar to each other with respect to age, weight, and height (table 3). The dose of local anesthetic used during surgery, the number of patients who were in labor at the time of their cesarean, and the number of patients undergoing repeat cesarean sections were also similar.

Analgesia following 50 μg of epidural sufentanil was of similar intensity, *i.e.*, similar decrease in visual analog pain score at 15 min, to that following 10 μg of iv sufentanil (fig. 2). However, duration of analgesia was significantly longer with epidural than with iv sufentanil (table 3). The precise time of onset of analgesia was not established, since pain was not evaluated until 15 min

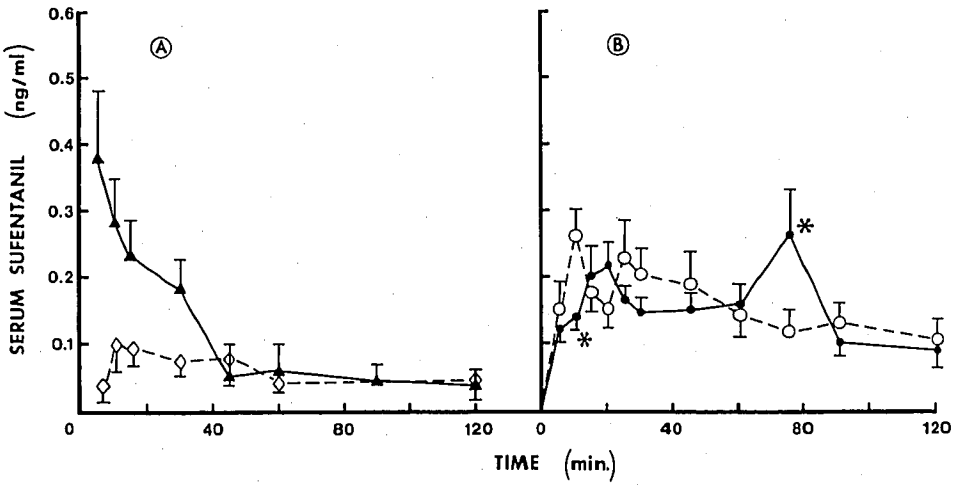

FIG. 1. Serum sufentanil concentrations (mean ± SEM) as a function of time. *A.* Sufentanil, 30 μg, iv (▲ —— ▲) and 30 μg, epidurally (◇ - - - ◇). *B.* Sufentanil, 50 μg, epidurally (○ - - - ○) and 50 μg + epinephrine, epidurally (● —— ●). *Significant difference between treatment groups.

TABLE 2. Phase I: Numbers of Patients with Side Effects in Each Sufentanil Treatment Group

	Intravenous 30 μg (n = 6)	Epidural 30 μg (n = 6)	Epidural 50 μg (n = 6)	Epidural 50 μg + Epinephrine (n = 5)
Sedation	6	1	5	2
Nausea	2	2	3	1
Vomiting	2	1	0	1
Pruritus	2	1	2	3
Respiration depression	1	0	0	0

TABLE 3. Phase II: Patient Characteristics and Analgesic Properties

	IV-10 (n = 20)	EPI-50 (n = 20)
Age (yr)	30 ± 1	30 ± 1
Height (cm)	163 ± 3	160 ± 3
Weight (kg)	80 ± 4	78 ± 5
Duration of analgesia (min)	96 ± 15	232 ± 24*

Values are mean ± SEM. IV-10 = intravenous sufentanil, 10 μg; EPI-50 = epidural sufentanil, 50 μg.
* $P < 0.0001$.

after sufentanil injection, by which time all patients with the exception of three in the iv group had marked pain relief. Pain scores did not change significantly between 15 and 30 min. The requirement for supplemental (PCA) sufentanil in the first 12 h was only 85 ± 2 μg following epidural sufentanil (EPI-50 group), as compared with 122 ± 11 μg following iv sufentanil (IV-10 group) ($P < 0.01$). However, when the initial sufentanil injection is included, the total dosage in the first 12 h was the same in both groups (EPI-50: 135 μg, and IV-10: 132 μg). In the period from 12–24 h after study drug administration, there was no difference in sufentanil usage between the groups (EPI-50: 111 ± 15 μg *vs.* IV-10: 115 ± 16 μg).

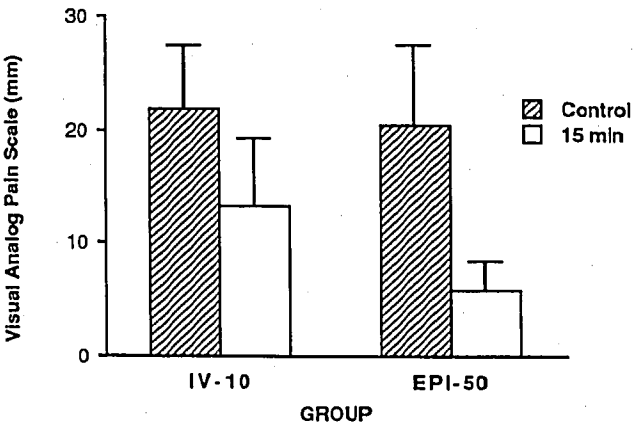

FIG. 2. Visual analog pain score before, and 15 min after, administration of sufentanil (IV-10 = intravenous sufentanil, 10 μg; EPI-50 = epidural sufentanil, 50 μg). Values are mean ± SEM.

The groups also were similar with respect to the maximum increase in sedation score measured at 15–30 min (fig. 3). Neither respiratory depression nor hypotension was observed in any patient as a result of the initial treatment. The incidence of side effects reported in the first hour after study drug administration is summarized in table 4. Nausea and vomiting were always mild or moderate. Pruritus was mild, except for two patients in the epidural group who complained of severe itching.

DISCUSSION

The high incidence of side effects with epidural morphine and other opioids with low lipid solubility led to the suggestion that the newer, more lipid-soluble agents might have a more rapid onset and be safer and more efficacious.[1] Satisfactory analgesia following cesarean section was obtained with epidural administration of fentanyl, 50–75 μg, but its duration was considerably less (2–4 h)[6] than that of morphine (12–24 h).[7,8] Studies in experimental animals have indicated that epidurally administered sufentanil might be both more potent and longer acting than fentanyl.[9,10] However, because sufentanil is more lipid soluble than morphine, it may result in greater systemic absorption, which might produce side effects soon after injection.

Our data demonstrated rapid absorption of sufentanil following both epidural and intravenous administration. Given the high lipophilicity of sufentanil, it is not surprising that it is rapidly absorbed after epidural injection. However, it raises a question as to whether the primary analgesic effect of epidurally administered sufentanil is due to a systemic or a spinal action. Following iv sufentanil, analgesia persisted for about 60 min once serum levels had become undetectable (<0.1 ng/ml), whereas it persisted for 80–140 min in the epidural groups with similarly undetectable levels. This suggests that the analgesic properties of epidural sufentanil are due, in part, to a spinal action of the opiate.

In studies involving rats, Colpaert *et al.*[11] similarly demonstrated significant plasma concentrations following both epidural and iv sufentanil. They reported essentially equipotent analgesic effects with both routes of administration, but found less pharmacologic activity originating from cerebral sites and less binding in most areas of brain tissue following epidural than following intravenous administration. Also, the relatively greater degree of binding to mu-receptors in the spinal cord at low epidural doses, as compared with similar intravenous doses, supports a spinal site of action. Nevertheless, it is likely that systemic absorption contributes to the analgesic effect of epidural sufentanil, particularly in the period immediately after administration. The ad-

dition of epinephrine may contribute to a delayed absorption of sufentanil; however, it does not produce a significant prolongation of its analgesic effects.

With respect to clinical efficacy, both epidural and iv sufentanil produced a rapid onset of analgesia. Although the maximal intensity of analgesia was similar with both routes of administration, the duration of pain relief was longer with epidural than with iv sufentanil. This difference in duration might be explained by the fact that larger doses were injected epidurally than intravenously. This is unlikely to be the sole explanation, however, since analgesia with iv sufentanil was not significantly more prolonged following the 30-μg dose than following the 10-μg dose (108 ± 20 min *vs.* 96 ± 15 min). In fact, our study design would have tended to underestimate the difference in duration of effect between the two routes of administration for two reasons. Firstly, since all patients in Phase I and most in Phase II received sufentanil intraoperatively, the duration of analgesia recorded with iv sufentanil would have reflected in part the residual analgesia resulting from the epidural lidocaine. Secondly, chloroprocaine was used to supplement the epidural block in 35–45% of all patients. Since this agent has been reported to impair the efficacy of epidurally administered narcotics,[12,13] it might have resulted in a shorter duration of analgesia with epidural sufentanil.

Our findings are consistent with those reported in other clinical studies of epidural sufentanil, in which a minimum dose of 30 μg has been found necessary to produce satisfactory analgesia following cesarean section, thoracotomy, and orthopedic surgery.[14–17] In some of these studies,[14,15,17] increasing the sufentanil dosage to 60–75 μg produced little or no improvement in quality or duration of analgesia. This "ceiling effect" for analgesia has been reported with other epidurally administered narcotics,[6] and may relate to saturation of opiate receptors in the spinal cord. Although sufentanil and fentanyl have not been directly compared with one another in a clinical study, the analgesia resulting from 25–50 μg of epidural sufentanil appears similar to that resulting from 50–100 μg of epidural fentanyl. Thus, the potencies of sufentanil and fentanyl appear different when they are administered by the epidural route (relative potency about 1–2:1) than when they are administered by the intravenous route (relative potency 7–10:1).

Serious side effects did not occur in our patients with epidural sufentanil at any dosage. Drowsiness was a common side effect of sufentanil, and was most marked with the 30-μg iv and the 50-μg epidural doses. Sedation was minimal with the 30-μg epidural dose, possibly related to the lower plasma concentrations in this group (fig. 1). Duckett *et al.*[15] and Donadoni *et al.*[16] found that

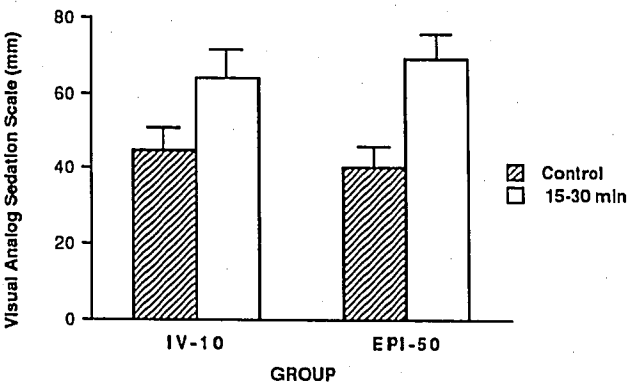

FIG. 3. Visual analog sedation score before, and 15–30 min after, administration of sufentanil (IV-10 = intravenous sufentanil, 10 μg; EPI-50 = epidural sufentanil, 50 μg). Values are mean ± SEM.

drowsiness occurred in all patients who obtained satisfactory analgesia with epidural sufentanil.

Respiratory depression was not observed following epidural sufentanil in our study, or in other studies involving cesarean section or orthopedic surgery patients.[14,16] However, Whiting *et al.*[17] demonstrated severe respiratory depression in post-thoracotomy patients following 20-ml epidural injections containing 30, 50, or 75 μg of sufentanil. In that study, dose-related ventilatory depression occurred 10–38 min following epidural administration. This could have been a consequence of systemic absorption of sufentanil, or of direct venous transit of the narcotic to the respiratory center *via* the epidural plexus of veins. Alternatively, sufentanil may have ascended rapidly in the CSF to the respiratory center. The use of a relatively large volume of diluent (20 ml) in the study of Whiting *et al.*[17] may have accelerated cephalad spread along the neuraxis. In addition, residual effects of general anesthesia, and ventilatory impairment secondary to the operation itself may have made their patients more susceptible to the respiratory depressant effects of sufentanil.

In summary, both intravenous and epidural sufentanil provided a rapid onset of analgesia, the duration of which was longer following epidural administration

TABLE 4. Phase II: Numbers of Patients with Side Effects in the First Hour Following Study Drug Administration

	IV-10 (n = 20)	EPI-50 (n = 20)
Nausea	5	5
Vomiting	1	2
Pruritus	1	8*
Respiratory depression	0	0

IV-10 = intravenous sufentanil, 10 μg; EPI-50 = epidural sufentanil, 50 μg.
* $P < 0.05$.

(3–4 h) than following intravenous administration (1–2 h). Increasing the dose of sufentanil by either route did not significantly prolong analgesia, and is not recommended because of the possibility of respiratory depression secondary to higher plasma concentrations. Although epidural sufentanil has a relatively short duration of effect, its rapid onset makes it an ideal agent for supplementing epidural local anesthetic analgesia (for example, during exteriorization of the uterus during cesarean section), or for initiating analgesia in patients experiencing acute postoperative pain prior to administration of a longer-acting narcotic. Our preliminary data would suggest that epidural sufentanil, 30 μg, provides adequate postoperative analgesia with minimal narcotic-induced side effects.

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Repeated Anesthesia for a Patient With Neuroleptic Malignant Syndrome

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Since Delay and Deniker first described the neuroleptic malignant syndrome (NMS) in the English language as a potential complication of using neuroleptics,[1] approximately 300 cases have been reported.[2,3] Signs of NMS, which appear over a 24–72-h period, include muscular rigidity, hyperthermia, altered level of consciousness, and autonomic instability (manifested as tachycardia, labile blood pressure, diaphoresis, and incontinence). The syndrome occurs hours to months after known exposure to neuroleptics, such as haloperidol, fluphenazine, and thiothixene. It has been said that NMS is underdiagnosed and that the frequency is as