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Intrathecal Sufentanil Compared to Epidural Bupivacaine for Labor Analgesia

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Background: **Although intrathecal sufentanil has been reported to provide rapid-onset, complete analgesia lasting 1–3 h for the first stage of labor, no well-controlled double-blind study has compared this technique to the use of epidurally administered local anesthetics.**

Methods: **Fifty healthy parturient women requesting labor analgesia were studied. In a combined spinal–epidural technique, a spinal needle was inserted through the epidural needle before insertion of the epidural catheter. Patients were randomly assigned to receive either intrathecal sufentanil (10 μg) and epidural saline, or intrathecal saline and epidural bupivacaine (30 mg). Visual analog scores for pain, blood pressure, heart rate, sensory levels, and the incidence of nausea, pruritus, and motor blockade were recorded.**

Results: **Patients receiving intrathecal sufentanil had significantly lower visual analog pain scores at 5, 15, and 30 min after injection and a greater duration of analgesia before requesting additional medication (mean 123 *vs.* 68 min for those receiving bupivacaine; $P < 0.05$). These patients also experienced pruritus more frequently but motor blockade less frequently than patients receiving epidural bupivacaine. The groups exhibited dermatomal sensory deficits to pin prick as well as bradycardia and hypotension with equal frequency. The length of labor and type of delivery were similar between the groups. No patient experienced a post-dural puncture headache.**

Conclusions: **The rapid onset of analgesia and lack of motor blockade from intrathecal sufentanil injection may be advantageous in certain clinical situations. With this technique, however, pruritus is common; hypotension may occur; and extensive dermatomal spread suggests that early-onset respiratory depression could occur. Therefore, blood pressure and respiratory adequacy should be monitored if intrathecal sufentanil is used. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural; intrathecal. Anesthetics, local: bupivacaine. Anesthetics, opioid: sufentanil.)**

EPIDURALLY administered bupivacaine provides effective analgesia for the first stage of labor[1,2] but is often associated with maternal hypotension, which can reduce uterine perfusion, and with motor blockade, which may interfere with maternal expulsive forces.[3] These unwanted effects are due to the nonspecific neural blockade caused by bupivacaine. Epidural or intrathecal injection of opioids has the potential to provide "selective analgesia" without such effects. Intrathecal injection of sufentanil has been reported to provide excellent analgesia, lasting 1–3 h and without evidence of motor blockade or hemodynamic depression, for the first stage of labor.[4–6,§,‖,#]

The purpose of this study was to compare, using a randomized double-blind design, the analgesia and side effects of intrathecal sufentanil and epidural bupivacaine during the first stage of labor. Although intrathecal sufentanil has been compared to other intrathecal opioids[6,‖] and to epidural or intravenous sufentanil,[5] it has never been compared to epidurally administered bupivacaine, a standard obstetric analgesic. Because spinally administered opioids have been shown to decrease sympathetic outflow by an action in the spinal cord,[7–10] the effect of each treatment on blood pressure was monitored. Finally, because a rapid cephalad spread of intraspinally administered lipid-soluble opioids and morphine has been demonstrated,[11–13] we sought to monitor cephalad spread by sensory testing.

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Materials and Methods

The protocol was approved by the Clinical Research Practices Committee, and written consent was obtained from each patient. Fifty ASA physical status 1 or 2 parturient women with singleton pregnancies in the vertex presentation were enrolled in the study. All patients were para 0 or 1 and in active labor with cervical dilatation less than 7 cm when epidural analgesia was requested.

After an intravenous bolus of at least 250 ml lactated Ringer's solution, a 8.9-cm ($3\frac{1}{2}$-inch) 17-G Tuohy needle (Becton-Dickinson, Rutherford, NJ) was inserted into the epidural space at either the L2–L3 or the L3–L4 interspace by a loss-of-resistance technique with saline. A 11.9-cm ($4\frac{11}{16}$-inch) 25-G Whitacre or a 11.9-cm ($4\frac{11}{16}$-inch) 27-G Quincke needle (Becton-Dickinson) was then inserted through the epidural needle into the subarachnoid space, and a 2-ml intrathecal injection was administered. The spinal needle was removed, and an 18-G epidural catheter (Burron, Bethlehem, PA) (single distal port) was then inserted 3–5 cm into the epidural space and a 12-ml epidural injection administered in divided doses (2 ml followed in 3 min by 5 ml followed in 1 min by 5 ml). After epidural placement, patients were placed in the lateral position to achieve left uterine displacement.

Patients received, as determined by a table of random numbers, either intrathecal sufentanil or epidural bupivacaine. Those in the sufentanil group received an intrathecal injection of 10 μg sufentanil diluted in 2 ml preservative-free saline and an epidural injection of 12 ml preservative-free saline. Those in the bupivacaine group received a 2-ml intrathecal injection of preservative-free saline and 12 ml 0.25% bupivacaine (30 mg) epidurally. The study solutions were prepared by an anesthesiologist not involved in the patients' care, and both the patient and investigator were blinded to the study solutions.

Pain was assessed with a 10-cm linear visual analog score (VAS) immediately before spinal–epidural placement and 5, 15, and 30 min after injection of the first 2 ml of epidural solution. Because of physical limitations involved in insertion of the epidural catheter and administration of the epidural study solutions, 6 min elapsed between the intrathecal injection and the completion of the epidural injections. Additional VAS scores were obtained every 30 min until delivery of the baby or additional medication was requested. If the patient requested additional analgesia, 10 ml 2% lidocaine was administered epidurally and VAS scores obtained after 20 min. Patients experiencing no analgesia within 30 min of dosing were defined as having inadequate blocks and were excluded from the study. At the time of each VAS assessment, patients subjectively rated nausea, pruritus, and motor blockade as none, mild, moderate, or severe. Motor blockade was not objectively assessed by the investigators. Blood pressure, heart rate, and cephalad sensory changes (hypalgesia) to pinprick were ascertained at the same intervals as VAS scores. Patients rating pruritus as moderate or severe were offered treatment and given naloxone 40 μg intravenously if requested. A reduction in systolic blood pressure to more than 20% below baseline was treated with an intravenous fluid bolus; if this was ineffective, 10 mg ephedrine was administered intravenously and repeated as needed.

Blood pressure and heart rate were monitored with a noninvasive monitor (Accutorr 4, Datascope, Paramus, NJ) every 2.5 min for 20 min after any intrathecal or epidural injection and every 15 min thereafter. Baseline values for blood pressure and heart rate were the values obtained immediately before the procedure. Respiratory rate was recorded every 15 min throughout the study, and oxyhemoglobin saturation was monitored by pulse oximetry in all patients for 1 h after the intrathecal injection. Fetal heart rate and uterine activity were monitored continuously throughout labor. The duration of labor, total local anesthetic requirements, mode of delivery, and neonatal Apgar scores were recorded. All patients were contacted by telephone 1 week after delivery and questioned for the occurrence of a post–dural puncture headache.

Data are presented as means ± SEM. Groups were compared for continuous single variables by Student's t test and for noncontinuous variables or proportions by Fisher's exact test or chi-square analysis. Normally distributed groups were compared by two-way analysis of variance for repeated measures; within each group, the change from baseline was determined by one-way analysis of variance followed by Dunnett's test. Nonparametric data were compared by the Mann–Whitney rank-sum test. VAS pain scores were compared by the Kruskal–Wallis statistic followed by Dunn's test. The change from baseline was determined by the Mann–Whitney rank-sum test. The duration of analgesia was determined by Kaplan–Meier survival analysis followed by Wilcoxon's test. $P < 0.05$ was considered significant.

Results

Sixty-two patients were enrolled in the study; of these, 50 (25 receiving intrathecal sufentanil and 25 receiving epidural bupivacaine) completed the study and were included in data analysis. Cerebrospinal fluid (CSF) could not be obtained from 6 patients; 5 patients delivered precipitously within 30 min of epidural placement; and in 1 patient, intravenous epidural catheter insertion occurred during attempted epidural catheterization.

Treatment groups did not differ in demographic variables, VAS pain scores, parity, percentage receiving oxytocin, or cervical dilatation at the time of entry into the study (table 1). VAS pain scores were significantly less at the 5-, 15-, and 30-min time points in patients receiving sufentanil than in those receiving bupivacaine, but VAS pain scores were similar at 60 min (fig. 1). The mean duration of analgesia, defined as the time to a request for additional analgesia, was 68 min for patients receiving epidural bupivacaine *versus* 123 min for patients receiving intrathecal sufentanil ($P < 0.05$, fig. 2). VAS pain scores after redosing with 2% lidocaine were similar between the groups. The duration of first-stage labor after intrathecal injection, the duration of second-stage labor, and method of delivery were similar between the groups (table 1). Total bupivacaine administered during first-stage labor was significantly less for patients receiving intrathecal sufentanil (table 1).

Table 1. Patient Characteristics

	Sufentanil	Bupivacaine
Age (yr)	24 ± 0.9	25 ± 0.9
Height (cm)	165 ± 1.2	162 ± 1.2
Weight (kg)	80 ± 3.2	74 ± 2.8
Para 0	64%	76%
Para 1	36%	24%
Pitocin augmentation	12%	20%
Cervical dilatation (cm)	3.8 ± 0.3	3.8 ± 0.2
Baseline VAS scores	7.0 ± 0.5	7.8 ± 0.4
Stage 1 labor after intrathecal injection (min)	252 ± 33	199 ± 28
Stage 2 labor (min)	75 ± 15	107 ± 18
Total bupivacaine in stage 1 labor (mg)	84 ± 13*	133 ± 16
Spontaneous delivery	64%	64%
Instrumental delivery	16%	28%
Cesarean section	20%	8%

All values are mean ± SEM or percentage of 25 patients.

VAS = visual analog scale.

* $P < 0.05$ *vs.* bupivacaine group.

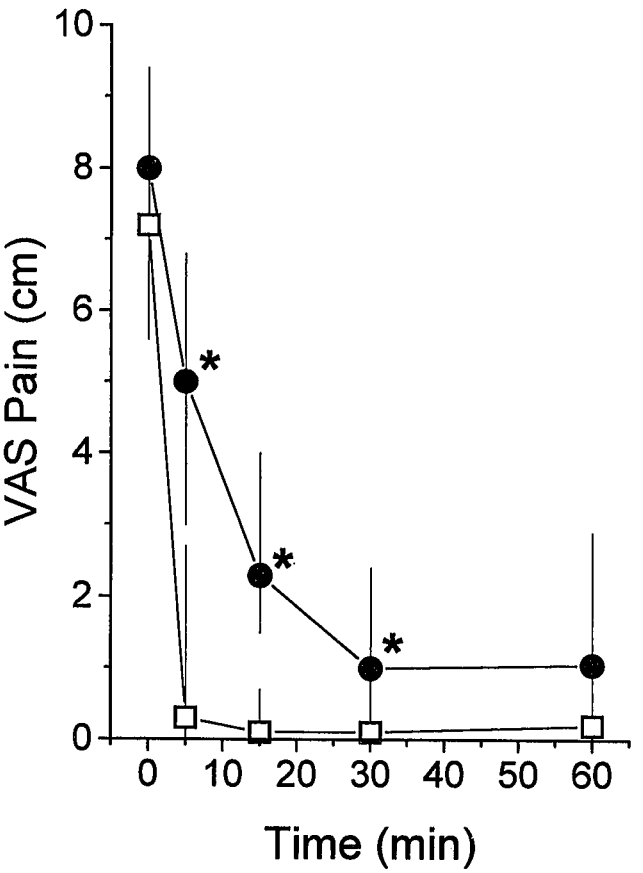

Fig. 1. Visual analog scale pain scores after injection of intrathecal sufentanil (squares) or epidural bupivacaine (circles). Time 0 is the time of the initial epidural injection. Sufentanil was injected at −2 min, and the total epidural dose was completed at +3 min. Each point represents the median ± 25th and 75th percentiles of 25 patients. All time points beyond baseline differ from their respective baseline values. *$P < 0.05$ *versus* sufentanil.

Significantly more patients in the sufentanil group than in the bupivacaine group experienced pruritus; three patients receiving sufentanil required treatment with intravenous naloxone (40 μg) (table 2). Significantly more patients receiving epidural bupivacaine experienced subjective motor blockade (table 2). The incidence of nausea, a reduction in heart rate greater than 20%, a reduction in blood pressure greater than 20%, and the use of ephedrine did not differ between groups (table 2). The groups did not differ in mean respiratory rate, and in no patient did respiratory rate decrease to less than 12 breaths/min. Oxyhemoglobin saturation was greater than 95% in all patients at all times. Neonatal Apgar scores did not differ between

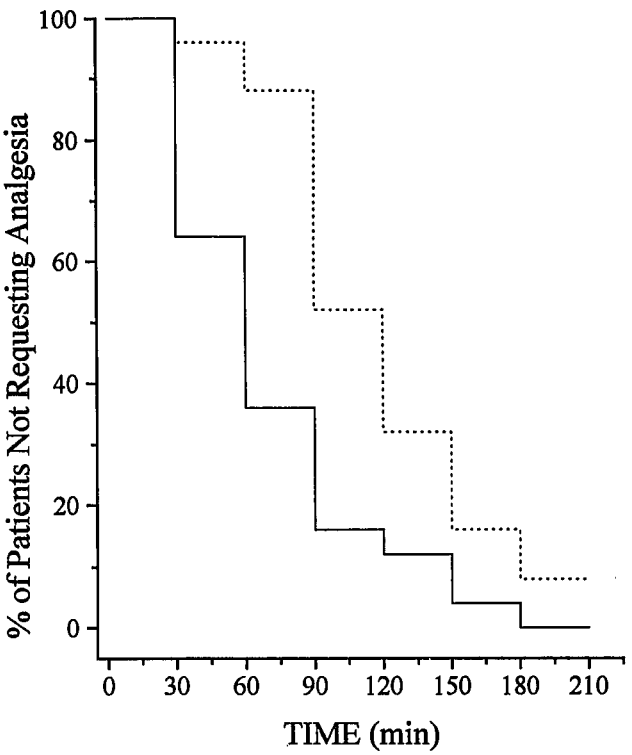

Fig. 2. Duration of analgesia, shown as the percentage of patients not requesting additional analgesia, after intrathecal injection of sufentanil (dotted line) or epidural injection of bupivacaine (solid line). The groups differ by Kaplan–Meier survival analysis followed by Wilcoxon's test.

groups, and no post–dural puncture headaches were reported within 1 week after dural puncture.

Blood pressure decreased to a similar degree in women receiving sufentanil as in those receiving bupivacaine (fig. 3, top). The average maximal decrease in mean arterial blood pressure was 15 ± 2% in those receiving sufentanil and 11 ± 2% in those receiving bupivacaine (*P* not significant). Eight patients in each group met clinical criteria for treatment of hypotension. In this subset of patients, blood pressure decreased sooner (within 5 min) in those receiving sufentanil than in those receiving bupivacaine (30 min) (fig. 3, bottom).

In all patients receiving bupivacaine, hypalgesia to pin prick developed, as it did 18 of 25 patients receiving sufentanil (fig. 4). No patient in the bupivacaine group achieved a sensory blockade more cephalad than T8. In contrast, five patients in the sufentanil group achieved a sensory blockade more cephalad than T4. In these five patients, upper cervical hypalgesia was observed to develop rapidly, reaching maximum cephalad spread at 15–30 min after injection (fig. 4).

Discussion

This is the first direct, double-blind comparison of epidural bupivacaine and intrathecal sufentanil for labor analgesia. In agreement with other studies,[4–6,14,15,§,‖,#] we observed rapid-onset analgesia with intrathecal sufentanil. However, in contrast to studies[4–6,§,‖,#] that found no hemodynamic depression or cephalad spread associated with intrathecal sufentanil, this study indicates that intrathecal sufentanil may be associated with hypotension and a rapid cephalad spread. These observations have also been recently reported by Grieco *et al.*[14] and Cohen *et al.*[15] and may have important implications for clinical practice and future research with this technique.

The rapid onset of analgesia (< 5 min) observed with intrathecal sufentanil may be explained by the high lipid solubility of sufentanil and is consistent with the results of several other studies.[4,5,14–16,§,‖,#] However, only for the first 30 min after injection were VAS pain scores for patients given intrathecal sufentanil significantly less than those for patients given epidural bupivacaine, suggesting an advantage in the use of intrathecal sufentanil in clinical circumstances in which rapid-onset analgesia is desired and the lack of motor blockade is desirable, *i.e.*, for multiparous women in whom labor is progressing rapidly late in the first stage. After 30 min, VAS pain scores were similar between groups. Thus, intrathecal sufentanil confers no advantage over epidural bupivacaine other than decreased motor blockade. In fact, the primary limitation of intrathecal sufentanil is the 123-min mean duration of action. Patients becoming uncomfortable would re-

Table 2. Side Effects

	Sufentanil (%)	Bupivacaine (%)
Pruritus	84*	0
Motor block	36*	84
Nausea	8	12
20% ↓ HR	36	12
20% ↓ BP	32	32
Ephedrine	12	12

All values are percentage of 25 patients.

HR = heart rate; BP = blood pressure.

* $P < 0.05$ *vs.* bupivacaine group.

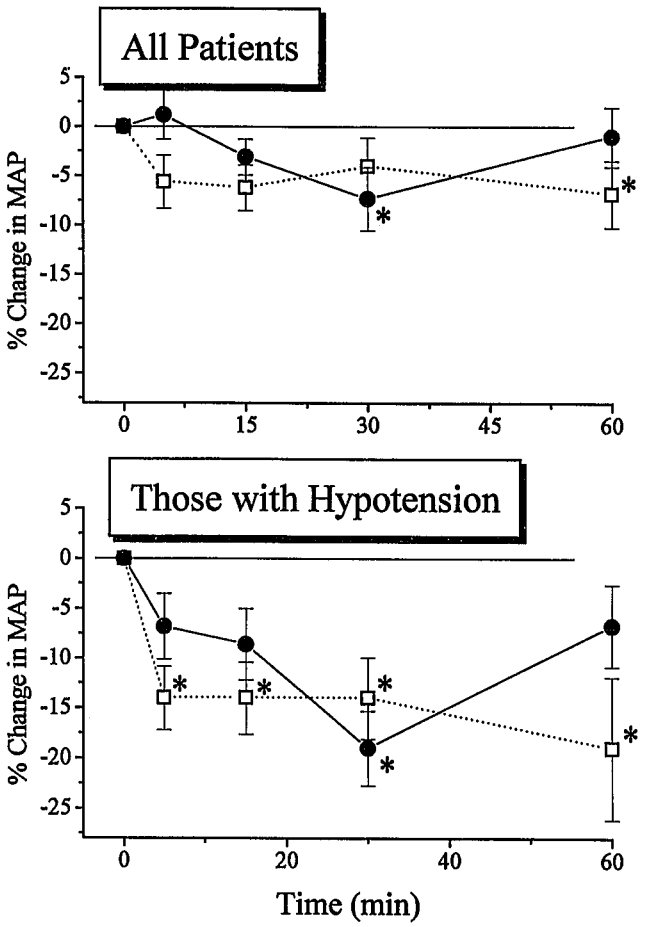

Fig. 3. Percentage change in mean arterial pressure (MAP) in all patients receiving intrathecal sufentanil (squares) or epidural bupivacaine (circles) (*top*) and in those meeting clinical criteria for treatment of hypotension (*bottom*). Each symbol represents the mean ± SEM of 25 patients (*top*) or 8 patients (*bottom*). *$P < 0.05$ *versus* baseline.

quire a second dural puncture, epidural placement, or implementation of epidural analgesia if a combined technique had been used. Therefore, intrathecal sufentanil would most appropriately be used with a combined spinal–epidural technique or in the clinical setting described above.

Reported advantages of intrathecal sufentanil include decreased local anesthetic use, which thereby decreases maternal and fetal exposure to local anesthetics, and lack of motor blockade, which thereby avoids potential interference with maternal pushing efforts and the normal descent of the fetus.[4–6] In this study, local anesthetic use was decreased by intrathecal sufentanil (table 1). Likewise, intrathecal sufentanil caused no motor blockade, and the groups did not differ in length of labor or mode of delivery (table 1). However, most patients in the sufentanil group did eventually receive local anesthetic, and therefore the affect of motor blockade on length of labor and mode of delivery could not be examined in those patients.

Our comparison of analgesia from these two techniques could be criticized on two grounds. First, VAS pain scores were not taken at identical time intervals: the 5-min VAS scores were obtained 5 min after the first 2-ml epidural injection, which averaged 7 min from the intrathecal injection and 1 min from the completion of the epidural injection. Despite this discrepancy, the time periods were chosen to mimic the clinical situation, and more time is required to thread an epidural catheter and administer incremental epidural

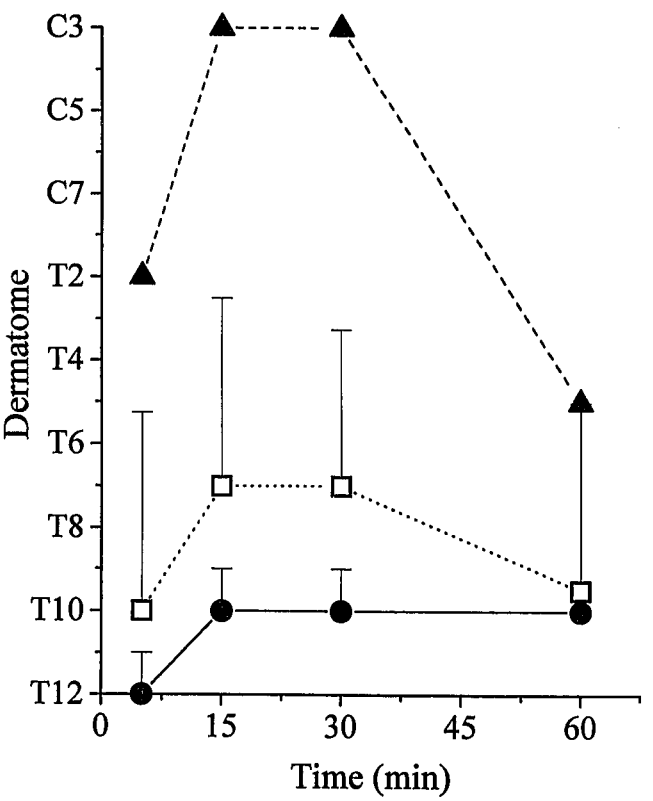

Fig. 4. Cephalad level of sensory blockade to pin prick in patients receiving intrathecal sufentanil (squares) or epidural bupivacaine (circles) or in the 5 patients receiving intrathecal sufentanil who achieved blockade more cephalad than T4 (triangles). Each symbol represents the median ± 75th percentile of 25 patients receiving bupivacaine, median ± 75th percentile of 18 patients receiving sufentanil, or the median of the subset of 5 of 18 patients receiving sufentanil with blockade more cephalad than T4.

doses than to administer a single intrathecal injection. Thus, intrathecal sufentanil 10 μg is associated with significantly better analgesia than epidural bupivacaine for the first 30 min after dosing under clinical conditions. Second, intrathecal sufentanil was compared to a single dose of epidural bupivacaine, which is not routine practice. Most patients receive some combination of repeated bolus injections or continuous infusions of local anesthetic after the initial epidural bolus of local anesthetic has been administered. That 10 μg intrathecal sufentanil provides longer analgesia than a single bolus of epidural bupivacaine offers little rationale for its selection alone, unless only 120 min of analgesia is desired during the first stage.

Contrary to our expectations, dermatomal hypalgesia to pin prick developed in 72% of patients receiving intrathecal sufentanil. In these patients, high thoracic and even cervical hypalgesia to pin prick developed rapidly (fig. 4). This implies rather extensive cephalad spread of sufentanil within the CSF. Although lipid-soluble opioids have generally been presumed to have a highly localized effect within the spinal cord, these data are consistent with several other studies that contradict this presumption.[11,12,16,17] Gourlay *et al.*[11] found high concentrations of fentanyl in cervical CSF within 30 min after lumbar epidural fentanyl injection in patients, and Stevens *et al.*[12] found high concentrations of sufentanil in cisternal CSF 21 min after lumbar epidural sufentanil injection in dogs. Furthermore, Weightman[18] reported a 0.6% incidence of respiratory depression in patients receiving epidural fentanyl infusion, similar to the 0.1–0.5% accepted incidence for intrathecal morphine. These findings support the hypothesis that epidural or intrathecal opioids spread rapidly within the CSF and so may lead to complications such as respiratory depression. In no patients in our study did oxyhemoglobin saturation decrease to less than 95%, but in light of the aforementioned risks, continuous pulse oximetry may be warranted as an easy, noninvasive method for indirectly monitoring respiratory depression in patients receiving intrathecal sufentanil.

The rapid rostral CSF spread of intrathecal sufentanil also may be related to the hemodynamic changes observed in some patients receiving intrathecal sufentanil. Hypotension (> 20% reduction from baseline), bradycardia (> 20% reduction from baseline), and hypotension requiring intravenous ephedrine were seen in this group, but they were observed just as frequently as in patients receiving epidural bupivacaine. Activation of opioid receptors on preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord reduces preganglionic sympathetic activity,[7–10] and intrathecal injection of morphiceptin, a highly selective μ-receptor agonist, causes dose-dependent reductions in mean arterial pressure and heart rate in rats.[10] Intrathecal sufentanil may have reduced blood pressure by affording pain relief of the preganglionic sympathetic opioid receptors, leading to decreased sympathetic tone. Although hemodynamic depression has only recently been reported as a common complication of intraspinal opioid injection in humans, sufentanil may be able to reach the relatively deep intermediolateral cell column because of its high lipid solubility, whereas less lipophilic opioids (morphine and fentanyl) may not reach these sites to cause hypotension. Alternatively, both treatments may have reduced blood pressure by affording pain relief. Nevertheless, it is important to note that hypotension did occur in patients receiving intrathecal sufentanil, and caution may be warranted when this technique is used for parturient women in whom hemodynamic stability is critical.

In summary, intrathecal sufentanil 10 μg offered a more rapid analgesia than epidural bupivacaine for the first 30 min after injection and caused no motor blockade; these characteristics may offer advantages in some clinical cases. However, hypotension was observed with equal frequency in those receiving intrathecal sufentanil and those receiving epidural bupivacaine, and rapid spread of the sensory blockade to upper thoracic dermatomes after intrathecal sufentanil injection suggests a rapid cephalad distribution in CSF. These results recommend caution in the use of this technique, with careful monitoring of blood pressure and respiration, especially during the initial 30 min after injection.

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