Intrathecal Sufentanil Dose Response in Nulliparous Patients


**Background:** Intrathecal sufentanil provides effective analgesia during the first stage of labor. A range of doses has been reported to provide adequate pain relief. This study determined the dose of intrathecal sufentanil that produced acceptable pain relief in 50% of nulliparous patients (ED₅₀) who requested labor analgesia.

**Methods:** With institutional review board approval, 50 nulliparous patients requesting spinal opioid labor analgesia were enrolled into this prospective, randomized, double-blinded study. Each patient was in spontaneous labor at <5 cm cervical dilation. Patients received one of the following doses of intrathecal sufentanil: 1, 2, 3, 5, or 10 μg in 3 ml preservative-free saline (n = 10 for each dose). Pain, pain relief, hemodynamic, respiratory, and side effect data were collected at times 0, 2, 5, 10, 15, 20, 25, and 30 min. Probit analysis of the number of patients in each group who requested additional pain medicine at 30 min was used to determine the ED₅₀.

**Results:** The groups were demographically similar. The ED₅₀ of intrathecal sufentanil was 1.8 μg (SE, 0.6 μg; 95% CI, 2.96 to 0.54 μg). The incidence of side effects was similar among the groups.

**Conclusions:** This is the first study to determine the ED₅₀ of intrathecal sufentanil in spontaneously laboring nulliparous patients. As dose–response curves are determined for other labor analgesics, future studies can compare equianalgesic doses or dose combinations. (Key words: Analgesia; obstetrics; opioids.)

**CLINICAL** studies of labor analgesia frequently compare the efficacy and side effects of different drugs and techniques without first determining that equipotent doses are being studied. For example, the dose of intrathecal sufentanil that produces pain relief in 50% of nulliparous parturients laboring spontaneously (ED₅₀) is unknown, but doses ranging from 3–15 μg have been reported to completely relieve labor pain.1–3 Authors comparing epidural and intrathecal labor analgesia have chosen an empirically derived dose of intrathecal sufentanil.4 The primary purpose of this study was to overcome this limitation by using the statistical treatment of probit analysis5 to determine the ED₅₀ of intrathecal sufentanil administered to nulliparous parturients in spontaneous early labor.

Although intrathecal sufentanil provides fast and effective relief of labor pain, its use is frequently associated with side effects. Pruritus and nausea and vomiting, usually transient and of mild to moderate severity, are reported by most authors.1,2,4,6,7 A decrease in maternal blood pressure and sensory changes, although reported less consistently, also can occur.2,8 In this study we...
recorded the incidence of these side effects after different doses of intrathecal sufentanil were administered.

Methods

Drug Preparation

All solutions were prepared by mixing 0.3 ml sufentanil (Janssen Pharmaceuticals, Piscataway, NJ) 50 μg/ml with 2.7 ml of preservative-free saline, creating a stock solution of 5 μg/ml sufentanil. Each dose was prepared using a 1-ml syringe to transfer the appropriate amount of stock solution into a 3-ml syringe. Preservative-free saline was added to each 3-ml syringe to a total volume of 3 ml. After enrolling a patient, the appropriate study solution was prepared according to a preprinted set of instructions. The physician preparing the study solution did not participate in data collection or in any decision regarding the timing of initial or subsequent analgesia.

The densities of 50 μg/ml sufentanil and normal saline at 37°C are hypobaric relative to the density of cerebral spinal fluid in full-term parturients. Therefore each parturient was placed in the lateral position during drug injection to standardize any effect of maternal position on the intrathecal spread of the injectate.

Study Protocol

After we obtained institutional review board approval, 24 full-term parturients classified as American Society of Anesthesiologists physical status 1 or 2 gave written informed consent to participate in this prospective, randomized, double-blinded study. All patients were nulliparous, in spontaneous labor with cervical dilation <5 cm, and had a single intrauterine pregnancy in the vertex position. Women who had received systemic analgesics or who were receiving oxytocin were excluded.

When patients requested analgesia, they were assigned to receive 2, 3, 5, or 10 μg intrathecal sufentanil (n = 6 in each group). Dose assignment was made by following a preprinted, sequentially numbered, computer-generated random list of the four drug doses. Initial data analysis, which occurred after data were collected from the first 24 patients, suggested an ED50 < 2 μg. Therefore, a 1-μg dose group was added (n = 10) and an additional four patients were added to each of the other dose groups for a total of 10 patients in each dose group. A second randomization list was generated and an additional 26 patients were enrolled.

Baseline values for blood pressure, room air oxygen saturation, respiratory rate, and visual analog scores for pain, nausea, and pruritus were obtained just before the patient was positioned for epidural placement. Each patient received a 250-ml intravenous bolus of balanced salt solution (Plasmalyte, Baxter Healthcare Corporation, Edison, NJ). Patients then assumed the left lateral position and, using an 18-gauge Hustead epidural needle (3.5 inches; B. Braun Medical Incorporated, Bethlehem, PA), the epidural space was identified using the loss-of-resistance technique. After placing a 24-gauge, 120-mm Sprotte spinal needle (Pajunk, Germany) through the epidural needle and obtaining clear cerebral spinal fluid, the assigned dose of intrathecal sufentanil was injected. After intrathecal drug injection, the spinal needle was withdrawn and an epidural catheter inserted for later use. The patients were placed at a 45° head-up position with left uterine displacement. The above variables and a pain relief visual analog score were recorded 2, 5, 10, 15, 20, 25, and 30 min after drug injection. Neither the patient nor the data collector was aware of the dose of drug administered. A decrease in systolic blood pressure to <100 mmHg or a decrease >20% from baseline indicated the need for treatment with ephedrine in 5-mg increments. At 30 min, sensory change to temperature was assessed using an alcohol wipe. Any patient who thought she had inadequate pain relief at 30 min received local anesthetic through the epidural catheter. Collection of pain relief data ended at 30 min because the maximum analgesic effect occurs between 20 and 30 min after intrathecal opioid injection. Pulse oximetry monitoring continued for 4 h after injection, with the lower limit alarm set at 94%. Nurses were instructed to notify anesthesia personnel immediately if the oxygen saturation rate decreased to less than this level. The time of patient request for additional analgesia was recorded.

All visual analog data were collected on 10-cm, horizontal, unmarked scales with the appropriate adjectives at each end (i.e., no pain, worst possible pain). For analysis each scale was measured from the left to right, with the left end of the scale equal to zero and the right end equal to 100 mm.

Fetal heart rate–uterine activity tracings from 20 min before to 30 min after injection were copied for subsequent analysis by a perinatologist. The perinatologist interpreting the data was unaware of the dose of study solution. Tracing analysis included baseline fetal heart rate, number of accelerations per 20 min, short-term variability, decelerations (variable, late, and early), and number of uterine contractions per 20 min. We defined
adequate short-term fetal heart rate variability as ≥6 beats/min and decreased short-term variability as <6 beats/min.

Patients were seen the next day and called at home 1 week after delivery to inquire about any postpartum problems, including headache.

Statistical Analysis

Statistical analysis was done on the data collected at the 30-min time point. Analysis of variance was used for normally distributed, continuous data, with Bonferroni’s t test for post hoc comparisons when significance was determined by analysis of variance. The Kruskal-Wallis test was used to compare non-normally distributed data (all visual analog scale data). Because patients were enrolled into this study during two separate periods, an additional comparison was made between the first and second groups of patients enrolled in the study, both as a group (first group vs second group) and within the 2-, 3-, 5-, and 10-μg doses. The primary outcome measure used to assess patient comfort was patient request for additional analgesia at 30 min. Probit analysis of the number of patients in each group who were comfortable at 30 min (time of maximal effect) was used to construct a logarithmic dose-response curve. The ED₉₀ and ED₅₀ values were defined as those doses required to make 50% and 95% of our patients comfortable at 30 min. We considered P < 0.05 significant.

Results

The patients in each group were demographically similar (table 1). Baseline pain scores did not differ among the groups (table 1). There were no demographic or baseline measurement differences between the original and subsequent study participants. Some pain relief was experienced by patients in each group at 30 min (fig. 1). Within the 2-, 3-, 5-, and 10-μg doses, there were no differences in pain relief data at 30 min between the original and subsequent group of patients. Patients in the 10-μg group were significantly more comfortable than patients in the 1-μg group at 30 min. Among the 18 patients who requested additional analgesia at 30 min, all had pain relief scores <80 mm (100 mm = complete pain relief). Of the remaining 32 patients who did not request additional analgesia, 31 of 32 had pain relief scores ≥80 mm. One patient, in the 3-μg group, had a pain relief score of only 10 mm and a pain score of 48 mm. This patient, however, did not request additional analgesia until 70 min after initial drug injection. For purposes of probit analysis, she was treated as a dose success. The calculated ED₉₀ in this patient population is 1.8 μg (SE, 0.6 μg; 95% CI, 0.96 to 0.54 μg) and the calculated ED₅₀ is 15.3 μg (SE, 13.9 μg; 95% CI, 6.1 μg to 6.9 μg; fig. 2).

Fig. 1. Pain relief visual analog scale versus time. Zero = no pain relief, 100 = complete pain relief. Data are mean ± SEM (error bars). *P < 0.05 versus 1 μg.
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Fig. 2. The percentage of patients comfortable at 30 min versus sufentanil dose (log scale). The dose of intrathecal sufentanil that produced acceptable pain relief in 50% of nulliparous patients ($ED_{50}$) = 1.8 μg (SE, 0.6 μg; 95% CI, 2.96 to 0.54 μg). The dose of intrathecal sufentanil that produced acceptable pain relief in 95% of nulliparous patients ($ED_{95}$) = 15.3 μg (SE, 13.9 μg; 95% CI, 654 μg to 6.9 μg). The $ED_{95}$ calculation involves extrapolation based on the probit model.

Pruritus occurred with similar intensity in each group (fig. 3). There was no change in respiratory rate. Blood pressure and peripheral oxygen saturation decreased slightly from baseline, but changes were similar in all groups at 30 min (figs. 4 and 5). The average nausea visual analog scores were <30 mm throughout the study. No patient required treatment for pruritus, nau-

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sea, or hypotension. One, three, four, six, and five patients in the 1-, 2-, 3-, 5-, and 10-μg groups, respectively, had detectable sensory changes to temperature at 30 min. The presence or absence of sensory changes to temperature did not correlate with maternal requests for additional analgesia at 30 min.

One patient in the 5-μg group had a 5-min decrease in oxygen saturation to 90–92% between 10 and 15 min after injection. The respiratory rate was 16 breaths/min during this time, with an increase to 24 breaths/min by 20 min when the episode resolved spontaneously. This patient had bilateral L1–L4 sensory levels to alcohol wipe at 30 min.

Data from the fetal heart rate–uterine activity tracings after intrathecal sufentanil injection are presented in table 2. No fetus experienced severe bradycardia. No neonate had an Apgar score <8 at 5 min.

Two patients in the 3-μg group and one patient in the 10-μg group reported mild positional headache after delivery. These patients experienced full resolution of their symptoms after treatment with oral ibuprofen and caffeine.

Discussion

Intrathecal sufentanil reliably produces dose-dependent analgesia in laboring patients. The current study determined that a dose of 1.8 μg produces pain relief in 50% of spontaneously laboring nulliparous patients at <5 cm cervical dilation. This finding is consistent with early reports that 3 μg intrathecal sufentanil provides adequate analgesia in some parturients. An ED₉₀ of 1.8 μg is slightly lower than the ED₉₀ of 2.6 μg (95% CI, 1.8 to 3.2) reported by Herman et al. Their study population, however, included multiparous and nulliparous patients in either spontaneous or induced labor who were at ≥6 cm cervical dilation. Parturients in slightly more advanced labor, who were receiving intravenous oxytocin, or who were experiencing more rapid labor, as in the case of a multiparous patient, would be expected to have a higher dose requirement to achieve adequate analgesia.

Many recent clinical studies of intrathecal labor analgesia in parturients have used a dose of 10 μg intrathecal sufentanil. Concordant with the results of this study, a 10-μg dose should produce pain relief in 90–95% of this patient population. Although the current study found an ED₉₀ of 15.3 μg, these data must be viewed with caution because the calculation of the ED₉₀ involves an extrapolation based on the probit model.

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Side effects after intrathecal sufentanil injection occurred with similar frequency in each group. Because of the sample size of this study, small, dose-related differences in side effects, if present, would not have been detected. Pruritus was a consistent finding. Although figure 3 suggests that pruritus may be dose related, the sample size of this study precludes any such conclusion. None of the patients in this study requested treatment for pruritus.

Blood pressure decreased slightly but significantly over time in each group. Analysis of variance showed no difference among the groups in the amount of this decrease. Some decrease in blood pressure can be expected purely from the provision of pain relief. The perceived degree of hypotension may be a function of the blood pressure used as the reference baseline. When the last prenatal blood pressure was used as the baseline, none of the 100 laboring parturients who received intrathecal sufentanil ± nalbuphine experienced a 20% or greater decrease in blood pressure. Nonetheless, intrathecal sufentanil can produce hypotension requiring treatment, necessitating blood pressure monitoring after injection.

Intrathecal μ-receptor agonists may produce mild hypotension directly, independent of the sympathetic nervous system. Women who receive 25 μg intrathecal fentanyl, after a 500-ml fluid bolus, can experience a decrease in blood pressure but with little change in end-diastolic index (preload) or stroke index. These results suggest that decreases in blood pressure are not sympathetically mediated. In rats, intrathecal injection of morphiceptin, a highly selective μ-receptor agonist, produces a dose-dependent decrease in blood pressure and heart rate. These responses are abolished by previous injection of intrathecal naloxone.

Detectable sensory changes to temperature were inconsistent and not related to intrathecal sufentanil dose. Although one to six patients in each group experienced sensory changes, only one or two in each group had bilateral change, with the rest having a one-sided band of decreased sensation. This finding is consistent with results reported by Riley et al., who found that the presence of sensory changes after intrathecal sufentanil were not predictive of the duration or quality of analgesia. The lipid-soluble opioids do exert weak, concentration-dependent, local anesthetic effects on mammalian peripheral nerves. The concentration required to produce a local anesthetic effect in a nonpregnant animal model (173 μM for sufentanil) is higher than that achieved clinically after 10 μg (1.04 μM) sufentanil. Sufentanil at a dose of 1.04 μM had no effect on conduction in rabbit dorsal root axons. Nonetheless, some parturients will have detectable sensory changes after intrathecal sufentanil injection. Given that male volunteers also develop sensory changes after intrathecal sufentanil, it is unlikely that sensory changes are pregnancy related.

Patients should be observed for respiratory changes after intrathecal sufentanil injection. Many patients had mild decreases in oxygen saturation. In one, this change was possibly of clinical significance. Intrathecal opioids produce respiratory depression by a direct effect on respiratory centers in the medulla. Lipid-soluble opioids can undergo very rapid cephalad spread after epidural injection. In a canine model, detectable levels of sufentanil in cisternal cerebrospinal fluid were present 1 min after epidural injection of 50 μg sufentanil in 5 ml saline. Peak cisternal levels, which were higher than plasma levels after 1 min, occurred 21 min after injection. If similar rapid cephalad spread occurs in humans, respiratory depression could occur relatively quickly after the intrathecal injection of a lipid-soluble opioid. Three case reports describe parturients who experienced respiratory depression shortly after receiving an intrathecal injection of a lipid-soluble opioid. Respiratory depression, although rare and usually mild, should be considered a potential side effect after the injection of intrathecal sufentanil.

In conclusion, intrathecal sufentanil reliably produces analgesia in spontaneously laboring nulliparous patients at <5 cm cervical dilation. A dose of 1.8 μg will result in pain relief in 50% of this population. This analgesia is accompanied by side effects that are typically self-limited or easily treated. To determine whether these side effects are dose-related will require further study. Additional studies of this type with other labor analgesics will result in more accurate comparisons among drugs and drug combinations used for labor analgesia.

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