Anesthesiology 2002; 96:1070–3

A Comparison of Intrathecal Fentanyl and Sufentanil for Labor Analgesia

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Background: **The use of intrathecal opioids for labor analgesia continues to gain popularity, but there are limited data to guide this use. Previously, the authors established the ED_{50} for 60 min of labor analgesia from intrathecal sufentanil using an up–down sequential allocation study design. The current study first establishes an ED_{50} for intrathecal fentanyl using this same study design to establish an intrathecal potency ratio for fentanyl and sufentanil and then uses this ratio to compare the efficacy, duration of analgesia, and side effects from comparable doses of intrathecal fentanyl and sufentanil.**

Methods: **Seventy-five healthy nulliparous women requesting labor analgesia were enrolled in this two-part study. In phase I, 20 women received varying doses of fentanyl to establish an ED_{50} for 60 min of labor analgesia. In phase II, 55 women were randomized to receive either 36 μg intrathecal fentanyl or 8 μg sufentanil (2 times the ED_{50}s) *via* a combined spinal–epidural technique and by double-blinded design. Pain relief, side effects, block height, maternal hemodynamics, and fetal heart rate were assessed throughout the study. The duration of spinal analgesia was considered to be the time from injection of study drug to the time of the patient's first request for additional analgesia.**

Results: **The ED_{50} of intrathecal fentanyl for 60 min of labor analgesia was found to be 18.2 μg, and therefore, the potency ratio of intrathecal sufentanil to intrathecal fentanyl at the ED_{50} level is 4.4:1. The duration of spinal analgesia was significantly longer from 8 μg intrathecal sufentanil than from 36 μg intrathecal fentanyl (104 ± 34 *vs.* 79 ± 34 min, $P = 0.009$). Otherwise, patient demographics, maternal hemodynamics, duration of labor, mode of delivery, motor block, subjective leg weakness, pruritus, nausea, pinprick sensory levels, visual analog scale pain scores, fetal bradycardia, and Apgar scores were similar between groups.**

Conclusion: **The relative potency of intrathecal sufentanil to fentanyl for labor analgesia is 4.4:1. When using intrathecal opioids alone for early labor analgesia, 8 μg sufentanil produces labor analgesia lasting approximately 25 min longer than from 36 μg fentanyl, without a statistically significant increase in side effects. However, when making a choice between fentanyl and sufentanil, one must consider other important factors, such as the higher cost of sufentanil and the greater risk of dosing error due to the higher potency of sufentanil compared with fentanyl.**

INTRATHECAL opioids are a popular choice for labor analgesia, with the synthetic opioids fentanyl and sufentanil being the most commonly used. The ED_{50} for sufentanil is well-established,[1–3] but only one study investigated the dose–response of fentanyl for labor analgesia.[4] Comparing the two to each other with existing data is difficult because relative potencies are unknown, and study designs vary. It is important to know what differences exist, if any, because the cost is significantly more for sufentanil, even in generic formulations. Also, it is more difficult to accurately measure a unit dose of sufentanil because of its relatively high concentration.

Therefore, the purpose of this study is twofold: (1) to estimate an ED_{50} for intrathecal fentanyl using previously reported methodology that estimated the ED_{50} for intrathecal sufentanil[1] and (2) to compare the efficacy, duration of analgesia, and side effects from comparable doses of intrathecal fentanyl and sufentanil based on ratios estimated from the ED_{50}s.

Materials and Methods

After approval by the Institutional Review Board and written informed consent, 75 healthy pregnant women were enrolled in this study. All patients were nulliparous, with American Society of Anesthesiologists physical status I or II, at term gestation, in active labor, and with a cervical dilation of 3–6 cm when requesting labor analgesia. Women were excluded who had received narcotic analgesics within 1 h of study initiation or had contraindications to regional anesthesia, weight greater than 114 kg, abnormal fetal heart rate tracing, or allergies to any study drug.

All patients received a combined spinal–epidural technique while in the lateral decubitus position. After placement of the epidural catheter, patients were positioned supine with left tilt. A 17-gauge Weiss epidural needle, a 27-gauge Whitacre 4 11/16-in spinal needle, and an 18-gauge closed-end, triple-port epidural catheter were used for each patient (Becton Dickenson, Franklin Lakes, NJ). All intrathecal injections in phase I were administered in a 1.5-ml volume with 5% dextrose in normal saline (D_5NS) as a diluent, to duplicate the methodology of the sufentanil study.[1] In phase II, all injections were administered in a 2.0-ml total volume with normal saline (NS) as a diluent, to more closely mimic actual clinical practice. To minimize mixing errors, detailed written instructions were attached to the randomization list, and the same three anesthesiologists not participating in patient care prepared the study solutions. The study solutions were prepared using 1-ml tuberculin (TB) syringes. The epidural catheter remained untested until the patients requested additional analgesia, but no sooner than 20 min after intrathecal injection.

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The study was performed in two parts. In phase I, we estimated the ED_{50} of intrathecal fentanyl by duplicating a previous study design that estimated an ED_{50} for intrathecal sufentanil.[1] In this study design, an effective dose was arbitrarily chosen as one that would provide 60 min of labor analgesia. The ED_{50} was established using an up–down sequential allocation design wherein each patent's dose was determined by the previous patient's response. Starting with an initial fentanyl dose of 22.5 μg, patient responses were categorized as a success, a failure, or a rejection. Patients who experienced more than 60 min of analgesia (4 or 5 pain relief on a 1–5 pain scale [1 = no pain, 2 = a little relief, 3 = half gone, 4 = almost gone, 5 = complete pain relief]) were categorized as successful. We chose to use pain relief scores rather than a specific "target" reduction in visual analog scale score because the latter can be affected by the initial visual analog scale score, whereas the former cannot. When a success occurred, the subsequent patient's dose was decreased by 2.5 μg. When a failure occurred (pain relief $<$ 4 on a 1–5 scale, or complete pain relief lasting $<$ 60 min), the subsequent patient's dose of fentanyl was increased by 2.5 μg. Patients were rejected when cervical dilation of 8 cm or greater was achieved within 60 min of spinal injection, in which case the same dose of fentanyl was repeated for the next patient. This rejection criterion was created to maintain homogeneity between groups because intrathecal opioids provide less effective analgesia for second-stage labor.

In phase II, the analgesic duration and side effects were compared between double the ED_{50} of sufentanil from our previous study and double the ED_{50} of fentanyl from phase I of the current study. In phase II, 55 women were randomly assigned to receive either 8 μg intrathecal sufentanil or 36 μg intrathecal fentanyl by double-blind design.

In phase II, pain was assessed using a 0–10 visual analog scale. Side effects, including pruritus, dizziness, nausea, sedation, and subjective leg weakness, were also assessed using a 0–10 scale (0 = none, 10 = worst imaginable). Pain and side effect scores were recorded at baseline; then pain relief, side effects, and sensory level to pin prick were recorded at 5, 10, 15, and 20 min after injection and at 30-min intervals thereafter until the patient requested additional analgesia. Maternal vital signs, fetal heart rate, and tocodynamometry were recorded throughout the study. All observations were made by an anesthesiologist or study nurse blinded to the treatment administered. The duration of spinal analgesia was considered to be the time from injection of study drug to the time of the patient's first request for additional analgesia, at which time the epidural catheter was tested, and labor analgesia was provided according to our standard clinical protocol.

Data from phase I were analyzed by the Dixon and Massey method to derive median effective doses (ED_{50}) with 95% confidence intervals. These data were also subjected to probit regression analysis as a back-up sensitivity test. Data from phase II were analyzed by analysis of variance and chi-square as appropriate. $P < 0.05$ was considered to be significant. Sample size estimates for phase I were based on previous data at our institution indicating that 20 patients would be required to achieve adequate power to determine the ED_{50} with a coefficient of variation of less than 20%. Sample size for phase II was estimated by power analysis to detect a 30-min difference in duration of analgesia between groups (SD, 32; power, 0.9; α, 0.05).

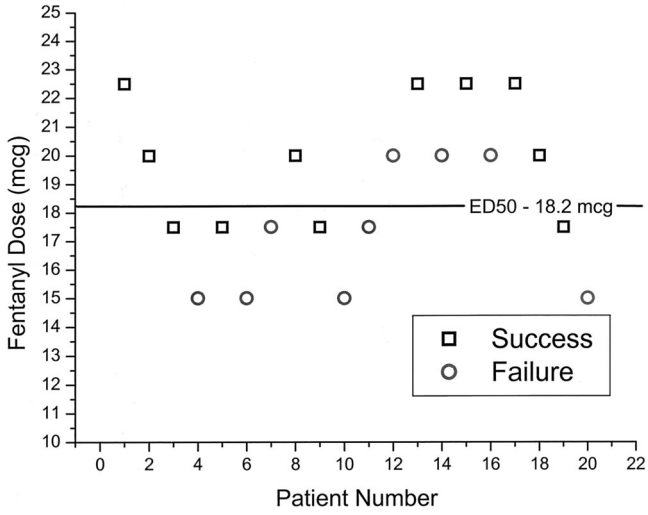

Fig. 1. Up–down sequential allocation for determining the ED_{50} of intrathecal fentanyl. The squares represent a success, whereupon the next patient received 2.5 μg less, and the circles represent a failure, whereupon the next patient received 2.5 μg more. The ED_{50} for 60 min of labor analgesia with intrathecal fentanyl is 18.2 μg.

Results

Phase I

Demographic variables were similar in patients experiencing successful and unsuccessful analgesia. The ED_{50} for intrathecal fentanyl was 18.2 μg (17.5, 18.8) by the Dixon and Massey method (fig. 1) and 18.2 μg (16.4, 20.1) by probit analysis. No patient had successful analgesia with 15 μg fentanyl, and no patient experienced unsuccessful analgesia with 22.5 μg fentanyl.

Phase II

Patient demographics and labor characteristics (cervical dilation at time of requesting labor analgesia, oxytocin use, mode of delivery, duration of labor from time of spinal injection to delivery, and pain scores before and after spinal injection) were similar between groups (table 1). Likewise, the incidence of maternal side effects (pruritus, nausea, hypotension, sedation, subjective leg weakness, and subjective dizziness) was similar between

Table 1. Patient Demographics and Labor Characteristics for Phase II

	Fentanyl (n = 29)	Sufentanil (n = 26)
Age (yrs)	25 ± 6	25 ± 5
Weight (kg)	65 ± 2	64 ± 2
Height (cm)	175 ± 21	172 ± 31
Cervical dilation (cm)	4 ± 1	4 ± 1
Mode of delivery (%)		
Vaginal, spontaneous	55	69
Vaginal, assisted	21	12
Cesarean delivery	24	19
VAS scores		
Before spinal injection	9 ± 2	9 ± 1
Lowest after injection	1 ± 2	1 ± 2

Unless otherwise indicated, data are presented as mean ± SD. There are no significant differences between groups.

VAS = Visual Analog Scale.

groups (table 2). The incidences of fetal bradycardia and Apgar scores were similar between groups, with a transient fetal heart rate decrease observed in one fentanyl patient and two sufentanil patients. The lowest Apgar scores (1 min/5 min) were 7/9 and 3/8 in the fentanyl and sufentanil groups, respectively. The duration of spinal analgesia was significantly longer from intrathecal sufentanil (104 ± 34 min) than from intrathecal fentanyl (79 ± 34 min, $P = 0.009$).

Discussion

The use of lipid-soluble synthetic opioids with the combined spinal–epidural technique for labor analgesia has several advantages over local anesthetic–based epidural analgesia. Fentanyl and sufentanil can safely provide effective, long-lasting labor analgesia without motor block, at a reasonable cost. Studies have now been published that can be used as clinical guidelines for dosing each of these drugs. For example, in one study, there seems to be no advantage to using 35 or 45 μg fentanyl over 25 μg as the sole intrathecal agent.[4] Perhaps a more accurate way of establishing guidelines, however, is to determine the ED_{50} for a drug. The main limitation to using comparisons between studies that determine the ED_{50}s is that the definition of the clinical end point of successful analgesia is not standardized. For example, the ED_{50} of intrathecal sufentanil ranges from 1.8 μg[2] to 2.6 μg[3] when the duration of successful analgesia is defined as 30 min. In contrast, we previously defined successful analgesia to be 60 min, and established an ED_{50} of 4.1 μg[1] for intrathecal sufentanil. Furthermore, results can be affected by other factors that vary from one study to another, such as study design and heterogeneous patient population. Therefore, before this study, no direct comparison between intrathecal fentanyl and sufentanil for labor analgesia could be accurately made. This is the first study to compare equipotent doses of intrathecal fentanyl and sufentanil for labor analgesia. Using identical study methods in the same patient population, we estimate that intrathecal sufentanil is 4.4 times more potent than intrathecal fentanyl at the ED_{50} level. This finding is similar to that of recent epidural studies, which also suggest that sufentanil is 4.5 times more potent than fentanyl.[5,6]

Table 2. Side Effects (%)

	Fentanyl (n = 29)	Sufentanil (n = 26)
Pruritus	83	85
Nausea	10	27
Hypotension	14	15
Sedation	41	58
Subjective leg weakness	34	58
Subjective dizziness	7	8

There are no significant differences between groups.

By administering double the ED_{50} doses to maintain the 4.4:1 ratio, intrathecal sufentanil produced significantly longer labor analgesia than intrathecal fentanyl. The reason for the longer duration of sufentanil is unclear but is most likely related to its inherent physiochemical properties when compared to fentanyl, such as its greater lipid solubility. However, it is also possible that the dose–response curves of fentanyl and sufentanil are not parallel, in which case we did not chose equipotent doses by doubling the ED_{50}s. A limitation of the up–down study design is that an ED_{95} cannot be reliably estimated. Assuming the dose–response curves are parallel for these similar lipid soluble synthetic opioids, we maintained the 4.4 potency ratio and doubled the ED_{50}s. The double ED_{50} doses are within the range of clinically acceptable doses reported in the literature.[2,3] Although Palmer[4] suggests that doses of intrathecal fentanyl greater than 25 μg are of little benefit, we chose to administer 36 μg to maintain the 4.4 potency ratio.

It is also interesting to note that although we find the relative potency of intrathecal fentanyl to sufentanil to be 1:4.4, this differs from the relative intravenous potency ratio of 1:9–10.[7,8] Because sufentanil is 8–10 times more lipid soluble than fentanyl, perhaps this difference in lipid solubility is less important when the drugs are administered intrathecally because they both have more direct access to the spinal nerves. Furthermore, they are being injected into the aqueous milieu of the cerebrospinal fluid, where lipid solubility would be expected to have less of a role in determining potency.

There are factors other than duration to consider when choosing spinal medications, one of which is cost. Currently, at our institution, the acquisition cost of sufentanil is 29.5 times as much as fentanyl ($7.08 *vs.* $0.24 for a 2-ml-ampule generic formulation). This can be an important issue in today's cost containment environment. For example, our current delivery rate is approximately 6,000 per year, with an epidural rate of approx-

imately 80%. With the increased cost per dose of sufentanil, this could translate to more than $32,000 of additional operating cost per year if each patient requesting analgesia received intrathecal sufentanil.

Another important issue to consider is patient safety. Both fentanyl and sufentanil are formulated with the same concentration (50 μg/ml), but sufentanil is 4.4 times more potent at the ED_{50} when administered intrathecally. An overdose resulting in severe respiratory depression and other side effects could occur if sufentanil were mistaken for fentanyl, but not *vice versa*. Also, it is somewhat difficult and time consuming to accurately measure and administer these small doses of sufentanil. This could lead to more dosing errors with sufentanil than with fentanyl. Based on this cost–benefit analysis, we believe the 25 min longer duration of spinal analgesia with intrathecal sufentanil does not outweigh the increase in cost and potential for dosing errors. Therefore, our current routine practice is to use fentanyl rather than sufentanil in the spinal portion of our combined spinal–epidural solutions. The difference in spinal analgesia duration is then overcome by starting the epidural infusion immediately after a negative spinal test dose. The rare parturient who delivers after fentanyl wears off and before sufentanil would have worn off and who has a nonfunctioning epidural catheter might benefit from the use of sufentanil. The individual anesthetist must decide if this potential benefit warrants the routine use of sufentanil despite its potential disadvantages. Also, our routine clinical practice includes the use of a local anesthetic, such as bupivacaine, in combination with opioid, and it remains to be seen whether the increased duration of sufentanil is still apparent when used in conjunction with bupivacaine.

In conclusion, we have established the relative potency for intrathecal fentanyl to sufentanil in labor analgesia to be 1:4.4 at the ED_{50} level, and at double the ED_{50} doses, sufentanil lasts 25% longer than does fentanyl without increasing side effects.

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