

## Intrathecal Sufentanil Produces Sensory Changes without Hypotension in Male Volunteers

Edward T. Riley, M.D.,\* Catherine L. Hamilton, M.D.,† Sheila E. Cohen, M.B., Ch.B., F.R.C.A.‡

**Background:** Intrathecally administered sufentanil is frequently associated with hypotension and sensory changes in women undergoing labor. In this study, the authors examined whether intrathecally administered sufentanil has similar effects in pain-free individuals with low concentrations of progesterone (*i.e.*, male volunteers).

**Methods:** Ten male volunteers were randomly assigned to receive an intrathecal injection of either 10  $\mu$ g sufentanil or saline in a double-blind fashion. Blood pressure, heart rate, oxyhemoglobin saturation, and temperatures from the body core and skin of the calf and ipsilateral great toe were recorded. Cold and pin prick sensation, motor block, and visual analogue scores for sedation, pruritus, and nausea also were assessed. Current perception thresholds using the Neurometer current perception threshold instrument (Neurotron, Inc., Baltimore, MD) were determined for three frequencies (2,000, 250, and 5 Hz, corresponding to stimulation of A $\beta$ , A $\delta$ , and C fibers, respectively) on the upper and lower extremities.

**Results:** Pruritus and sensory changes to pin prick and cold occurred in the sufentanil group but not the saline group. Neither group had a significant change in blood pressure, heart rate, oxyhemoglobin saturation, sedation, or core temperature. There was a clinically insignificant difference in the calf minus toe temperature index between the saline and sufentanil groups. There was a small increase in the current perception thresholds at 250 Hz in the sufentanil group.

**Conclusions:** Intrathecally administered sufentanil did not affect blood pressure in male volunteers. The other effects of sufentanil, however, were similar to those observed in women undergoing labor. This suggests that the hypotension oc-

curing in these women after intrathecally administered sufentanil is secondary to relief of pain, rather than to a sympathetomy. (Key words: Blood pressure changes; current perception threshold; obstetric analgesia; opioid analgesics; spinal opioids; sympathetic nervous system.)

THE lipid-soluble opioid agents sufentanil and fentanyl are frequently given intrathecally to provide analgesia during labor. Although they provide excellent pain relief, they have been associated with sensory changes, nausea, pruritus, and hypotension.<sup>1-3</sup> Although much of the research on intrathecally administered opioid agents has been performed in women undergoing labor, whether pregnancy and labor influence these phenomena is not known. High levels of progesterone similar to those found in the pregnant women potentiate the analgesic action of spinal opioid agents in an animal model.<sup>4</sup> Therefore, it is conceivable that the side effects commonly seen after intrathecally administered opioid agents in parturients are absent or less prominent in nonpregnant individuals. In one report in which 20  $\mu$ g of intrathecally administered sufentanil (ITS) was given to men and women for lithotripsy,<sup>5</sup> no mention was made of hypotension, nausea was absent, and pruritus occurred in only 27% of the patients.

Of particular interest to obstetric anesthesiologists is the hypotension that may occur after administration of ITS or fentanyl in women undergoing labor.<sup>1,2</sup> Whether the decrease in blood pressure results from a sympathetomy caused by weak local anesthetic action of sufentanil<sup>1</sup> or to pain relief remains controversial, although recent studies support the latter explanation.<sup>2,6</sup>

In the current study, we examined whether ITS causes hypotension, pruritus, sensory changes, or nausea in male volunteers. We selected this model to exclude the influence of labor pain and high concentrations of progesterone in the causation of these side effects.

### Methods

After obtaining approval by our human subjects review board and getting written informed consent, 10

\* Assistant Professor.

† Fellow, Obstetric Anesthesia.

‡ Professor.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Submitted for publication October 7, 1997. Accepted for publication March 19, 1998. Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 25, 1995.

Address correspondence to Dr. Riley: Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305. Address electronic mail to: edriley@Leland.Stanford.edu. No reprints will be available.

§ Moses M, Cascio M, Zakowski MI, Grant GJ: Hemodynamic effects of intrathecal fentanyl in term parturients (abstract). *ANESTHESIOLOGY* 1994; 81:A1150.



healthy, fasted, male volunteers (18- to 44-yr-old) were randomly assigned to receive an intrathecal injection of 10  $\mu$ g sufentanil diluted with saline to a volume of 2 ml ( $n = 5$ ) or 2 ml saline ( $n = 5$ ) in a double-blind fashion. Injections were made at the L2-L3 or L3-L4 interspace using a 24-gauge Sprotte needle. Intravenous access was established, but fluids were restricted to a maintenance infusion rate of lactated Ringer's solution. Participants breathed room air throughout the study. Data collected included systolic blood pressure, mean arterial pressure (using a Dinamap, Critikon, Tampa, FL), heart rate, respiratory rate, oxyhemoglobin saturation (using a Nelcor N1000 pulse oximeter, Nelcor, Hayward, CA), core temperature (tympanic membrane), and skin temperatures at the calf and ipsilateral great toe (measured with a Mon-A-Therm thermistor, Mallinckrodt, St. Louis, MO). Measurements were recorded just before the intrathecal injection, at 5-min intervals after injection for 30 min, and 45 and 60 min after injection.

Calf minus toe temperature (C-T) indices were calculated by subtracting toe temperature from calf temperature. Toe temperature is very sensitive to vasodilation compared with calf temperature, which is more constant. Therefore, a decrease in this index means that the toe has warmed relative to the calf and is an indication of vasodilation.<sup>7</sup> If toe temperature was not at least 4°C cooler than the calf before injection of the study drug, this indicated that there was already some vasodilation of the arterioles supplying the toes. In this circumstance, induction of a sympathectomy may not cause the toes to warm further. Therefore, these participants were excluded from this part of the analysis. The change in C-T index was calculated by subtracting the baseline index from the C-T indices at the various times after administration of the study drug. Cold and pin prick sensations were measured with an alcohol swab and a 25-gauge needle, respectively. Motor block was measured using a modified Bromage scale, in which 0 represented no motor impairment and 4 represented complete lower extremity motor block. Visual analogue scores were used to measure sedation (0-100, in which 0 was "completely awake" and 100 was "cannot keep my eyes open") and pruritus (0-100, in which 0 was "no itching" and 100 was "worst itching imaginable"). Nausea was measured on a 0-3 scale (in which 0 represented no nausea and 3 represented severe nausea). Evaluations were performed just before the intrathecal

injection and 5, 10, 15, 30, 45, and 60 min after the injection.

To examine the sensory changes associated with ITS more closely, current perception thresholds were determined using the Neurometer current perception threshold instrument (Neurotron, Inc., Baltimore, MD). Current perception thresholds were determined for three frequencies (2,000, 250, and 5 Hz) at two ipsilateral nerve sites at the hand and knee, before the block and 20, 40, and 60 min after the block. This device delivers a titratable sine wave electrical output at 5, 250, and 2,000 Hz that is purported to selectively stimulate C, A $\delta$ , and A $\beta$  nerve fibers, respectively.<sup>8,9</sup> The testing algorithm consisted of delivering an increasingly stronger current until the volunteer felt the stimulus. This was used as the starting current of the testing. The participant was then presented with 6 to 10 cycles of real and false stimuli above and below the starting current in a randomized, double-blind fashion until the current perception threshold was narrowed to approximately  $\pm 20 \mu$ A.

The theoretical but unsubstantiated basis of the Neurometer is that stimulation at the low frequency (5 Hz) causes only the C fibers to fire. The A $\delta$  and A $\beta$  fibers do not fire because the frequency is too low to stimulate them, but rather they accommodate to the slow wave stimulation and maintain their transmembrane potential. At 250 Hz, the A $\delta$  fibers fire, but the C and A $\beta$  fibers do not. As was the case at 5 Hz, the A $\beta$  fibers do not fire because the frequency is too slow to trigger them. The C fibers do not fire because the frequency of stimulation is too fast for them to respond. At 2,000 Hz, only the A $\beta$  fibers are able to respond.

Statistical analysis consisted of Student's *t* test for comparison of the demographic data, current perception thresholds, and change in sedation and pruritus scores; chi-square analysis to compare the incidence of sensory changes; and repeated-measures analysis of variance with Scheffé's *F* test for individual comparisons to compare changes in temperature, heart rate, and blood pressure over time. A probability value  $\leq 0.05$  was considered significant.

## Results

The groups did not differ regarding demographic or baseline data (table 1). Mean arterial pressure, heart rate, and respiratory rate did not change significantly



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Table 1. Demographic Data

|             | Intrathecal Sufentanil<br>(n = 5) | Intrathecal Saline<br>(n = 5) |
|-------------|-----------------------------------|-------------------------------|
| Weight (kg) | 83 ± 27                           | 73 ± 9                        |
| Height (cm) | 176 ± 7                           | 173 ± 5                       |
| Age (yr)    | 30 ± 10                           | 25 ± 8                        |

Values are mean ± SD. There were no significant differences between the groups.

from baseline in either group throughout the study period (fig. 1). Oxygen saturation did not decrease to <98% in any volunteer at any time during the study period. Sensation to cold decreased significantly in all participants receiving sufentanil at all times measured (upper dermatomal level range, L4-T8), whereas no subject in the saline group developed any change in sensation to cold. Sensation to pin prick was decreased after ITS in three of five participants (upper dermatomal

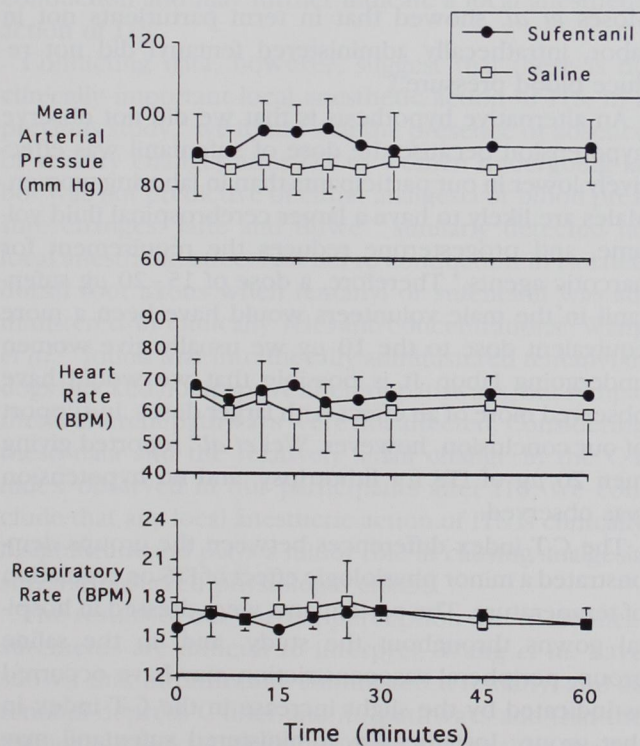


Fig. 1. Mean arterial pressure, heart rate, and respiratory rate in male volunteers after 10  $\mu$ g of intrathecally administered sufentanil or saline. Repeated-measures analysis of variance revealed no differences between the groups and no changes over time. Values are mean ± SD. Time 0 = preinjection values.

level range, L1-T7) beginning at 5 min and lasting until the end of the study period at 60 min. One person in the saline group transiently developed decreased pin prick sensation lasting 5 min. No participants in either group demonstrated any motor weakness.

All volunteers in the sufentanil group and four of five in the saline group had baseline C-T indices  $>4^{\circ}\text{C}$  (fig. 2), indicating that the arterioles supplying the skin of the toes were constricted. After administration of the study drug there was a small but statistically significant difference in the C-T indices between the two groups over time, because of a relative decrease in the C-T indices in the sufentanil group and a relative increase in the saline group. There was no significant change in

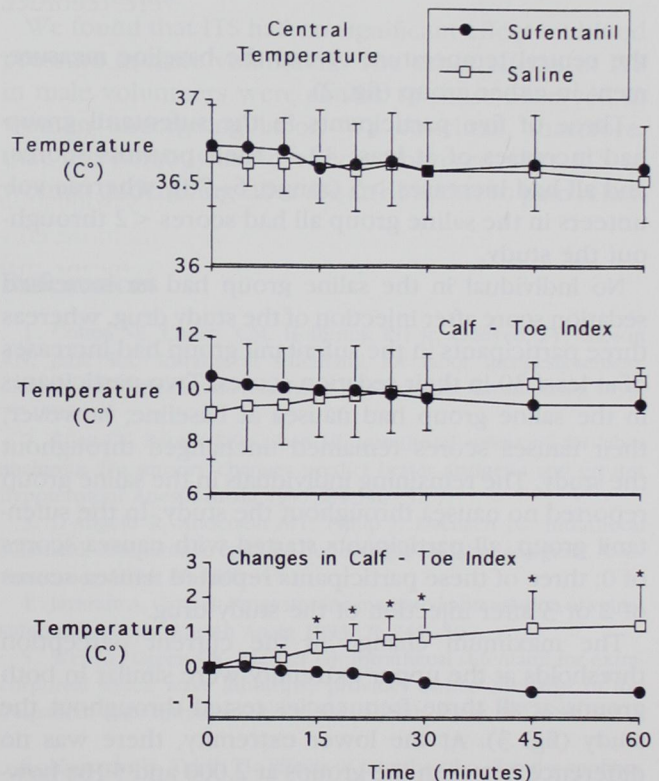


Fig. 2. Changes in central, toe, and calf temperatures and calf temperature minus toe temperature (C-T indices) in male volunteers after 10  $\mu$ g of intrathecally administered sufentanil or saline. Repeated-measures analysis of variance revealed a difference between groups over time when toe temperature was corrected back to zero (i.e., subtracting the baseline temperature from the temperature at each time interval). Intergroup comparisons were made using the Scheffé's F test. Values are mean ± SD. \*Significant difference between groups;  $P \leq 0.05$ .



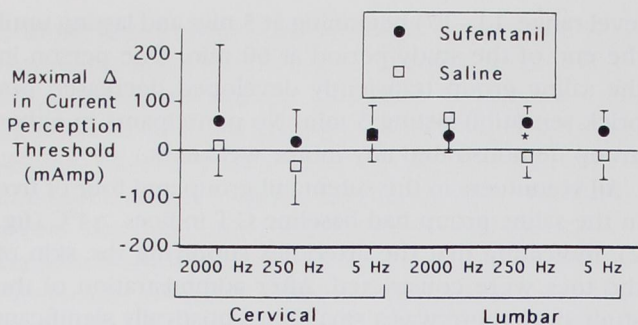


Fig. 3. Change in the current perception thresholds at 5, 250, and 2,000 Hz when tested over a cervical or lumbar dermatome in participants that received either intrathecally administered sufentanil or saline. Paired Student's *t* test demonstrated a significant difference between the groups at the lumbar site when stimulated at 250 Hz. Values are mean  $\pm$  SD.

the central temperature *versus* the baseline measurement in either group (fig. 2).

Three of five participants in the sufentanil group had increases of at least 32 in their pruritus scores, and all had increases  $>5$  (range, 6–70), whereas volunteers in the saline group all had scores  $<2$  throughout the study.

No individual in the saline group had an increased sedation score after injection of the study drug, whereas three participants in the sufentanil group had increases of at least 30 in their sedation scores. Two participants in the saline group had nausea at baseline; however, their nausea scores remained unchanged throughout the study. The remaining individuals in the saline group reported no nausea throughout the study. In the sufentanil group, all participants started with nausea scores of 0; three of these participants reported nausea scores of 2 or 3 after injection of the study drug.

The maximum change in the current perception thresholds at the upper extremity were similar in both groups at all three frequencies tested throughout the study (fig. 3). At the lower extremity, there was no difference between the groups at 2,000 and 5 Hz; however, at 250 Hz, the current perception thresholds were significantly increased after injection of the study drug (fig. 3).

|| Newman LM, Wlodarski JC, Tanck EN, Ivankovich AD: Neither intrathecal sufentanil nor intrathecal sufentanil plus nalbuphine cause hypotension in laboring patients (abstract). *ANESTHESIOLOGY* 1994; 81:A1153.

## Discussion

In pain-free male volunteers who have low levels of progesterone, ITS frequently caused pruritus and sensory changes, as is the case in women undergoing labor. The hypotension observed after ITS in patients undergoing labor, however, was not observed in this study. We observed no change in the blood pressure in the participants in the sufentanil group. Although the sample size was not large enough to make a definitive statement, these findings suggest that the hypotension that occurs in laboring women after ITS is secondary to the acute onset of pain relief. This conclusion is supported by other studies.<sup>2,6</sup>|| Nagasaka and Yaksh<sup>6</sup> found that rats placed on a hot plate had increased heart rate and blood pressure in response to the painful stimulus. If the animals were pretreated with intrathecal  $\mu$  agonists, however, the hemodynamic response was blunted. Our group<sup>2</sup> and others|| have observed no hypotension with ITS given during labor when blood pressure is compared with prelabor rather than with preanalgesia values when the patient is experiencing pain. In addition, Moses *et al.* showed that in term parturients not in labor, intrathecally administered fentanyl did not reduce blood pressure.<sup>5</sup>

An alternative hypothesis is that we did not observe hypotension because the dose of sufentanil was effectively lower in our participants than in laboring women. Males are likely to have a larger cerebrospinal fluid volume, and progesterone reduces the requirement for narcotic agents.<sup>4</sup> Therefore, a dose of 15–20  $\mu$ g sufentanil in the male volunteers would have been a more equivalent dose to the 10  $\mu$ g we usually give women undergoing labor. It is possible that we would have observed more of an effect with larger doses. In support of our conclusion, however, Wei *et al.*<sup>5</sup> reported giving men 20  $\mu$ g of ITS for lithotripsy, and no hypotension was observed.

The C-T index differences between the groups demonstrated a minor physiologic effect of ITS on regulation of temperature. The participants were dressed in hospital gowns throughout the study, and, in the saline group, peripheral vasoconstriction may have occurred as indicated by the slight increase in the C-T index in that group. Intrathecally administered sufentanil may have prevented this vasoconstrictive response to the ambient temperature and perhaps caused some additional decrease in the C-T index. Although statistically significant, this difference between the groups is clinical.



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cally insignificant. This change in the C-T index is minute compared with that seen after the administration of local anesthetic agents, which approximates 5–10°C.<sup>10</sup> The small decrease in the C-T index in this study and the lack of change in blood pressure suggest that ITS has a small physiologic effect regarding vasodilation. The cause for this remains unclear. One likely explanation is that ITS lowers the set point for the vasoconstrictive response to cold, just as occurs with intravenously administered opioid agents.<sup>11</sup> Alternatively, ITS may have some mild local anesthetic effect that decreases sympathetic outflow. Fentanyl and sufentanil depressed nerve conduction when isolated nerve preparations were bathed in supraclinical doses (50 and 100 µg/ml).<sup>12,13</sup> The sensory changes observed after ITS in this study and other investigations<sup>1,2</sup> also suggest a local anesthetic effect, which appears to be similar in pregnant and nonpregnant individuals. Further, current perception thresholds in this study demonstrated decreased sensitivity to stimuli at 250 Hz in the lumbar distribution. This could be because of decreased nerve conduction and may further indicate a local anesthetic action of ITS.

Conflicting data, however, suggest that there is no clinically important local anesthetic action of ITS. In a previous study,<sup>2</sup> we found that the presence or absence of sensory changes after ITS to women undergoing labor was not predictive of either analgesia or blood pressure changes. Jaffe and Rowe<sup>14</sup> similarly detected no local anesthetic effects on nerve conduction in isolated dorsal root axons when fentanyl or sufentanil was administered in clinically relevant concentrations. Wang *et al.*<sup>15</sup> found that intrathecally administered fentanyl in dogs blocked nociceptive afferent pathways, but sympathetic efferent pathways were not affected. Considering these data and the relatively small change in the C-T index observed in our participants after ITS, we conclude that any local anesthetic action of ITS is clinically insignificant and plays a minor role in causing analgesia and the observed physiologic effects.

The results of our current perception threshold measurements are difficult to interpret. Wang *et al.* have shown that intrathecally administered fentanyl and alfentanil depress C fiber and A $\delta$  pathways and that the former is more sensitive to opioid agents than the latter.<sup>15,16</sup> Therefore, the predicted current perception threshold results are that there should be an increased threshold at 5 and 250 Hz, with the greater effect at 5 Hz. Additionally, if ITS is acting segmentally, then

the lower extremity should be affected to a greater degree than the upper extremity. The only significant difference between the groups was that the current perception threshold was higher in the lower extremity when stimulated at 250 Hz. Why the current perception thresholds at 5 Hz were unaffected is unclear. The finding that the current perception threshold in the lower extremity was affected but the upper extremity was unaffected supports the hypothesis that ITS is acting segmentally. It should be noted, however, that the one statistically significant change in the current perception threshold was small in magnitude. Given that we recorded sensory changes to pin prick and temperature in many of the participants in the sufentanil group suggests that clinical measures are more sensitive than the current perception threshold measurements.

We found that ITS had no significant effect on blood pressure in male volunteers. The other effects of ITS in male volunteers were similar to those observed in women undergoing labor. We conclude, therefore, that the hemodynamic effects observed after ITS in women undergoing labor are attributable to pain relief.

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