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A Comparison of Intrathecal, Epidural, and Intravenous Sufentanil for Labor Analgesia

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A number of recent studies have suggested that the analgesic effects of highly lipid-soluble opioids are similar when these agents are administered either epidurally or intravenously. We sought to test whether the lipid-soluble opioid sufentanil was more effective when administered intrathecally than when administered epidurally or intravenously. Twenty-four women during active labor received sufentanil 10 μg either intrathecally (n = 9), epidurally (n = 8), or intravenously (n = 7), using a combined spinal–epidural technique. The sufentanil was administered alone, without concomitant local anesthetics. Analgesia was assessed using the visual analogue score as well as the time elapsed from the administration of study drug to the patient's request for additional analgesia *via* the epidural catheter (bupivacaine 0.25%). The median duration of analgesia (median, interquartile range) was 84 (70–92) min in the intrathecal group, 30 (23–32) min in the epidural group, and 34 (17–30) min in the intravenous group ($P < 0.001$). The intrathecal group showed rapid and significant decrease in visual analogue scale scores, whereas visual analogue scale scores in the other two groups did not decrease and remained significantly elevated compared to those of the intrathecal group at all observation points. Side effects were limited to pruritus in 3 patients (2 moderate and 1 severe) in the intrathecal group. No patient developed post–dural puncture headache. We conclude that sufentanil 10 μg intrathecally provides rapid and effective analgesia of 1–2-h duration during labor. Epidural and intravenous use of this dose of sufentanil did not provide evidence of satisfactory analgesia. Increased efficacy after intrathecal injection of sufentanil 10 μg suggests a spinal site of action by this route. (Key words: Analgesics: opioid; sufentanil. Anesthesia: obstetric. Anesthetic techniques: epidural; intrathecal; intravenous. Pain: labor.)

THE USE OF EPIDURAL and intrathecal opioids has become widespread. In particular, the epidural administration of opioids has gained great popularity in various clinical settings as a sole analgesic agent or as an adjunct to low-dose local anesthetic regimens.[1] Recently, a number of investigators have questioned whether the route of administration (epidural *vs.* parenteral) affects analgesic efficacy. Several highly lipid-soluble opioids have been found to have nearly identical analgesic profiles when injected either epidurally or parenterally, thus raising the question as to site of action (spinal cord *vs.* supraspinal) of these agents by these routes.[2–8]

All of the above-cited studies have compared epidural to parenteral administration of opioids. None has included intrathecal agents in its study design. Two recent preliminary reports have claimed that intrathecal administration of sufentanil can provide rapid and effective pain relief during labor.[9,10] We conducted this study to compare intrathecal, epidural, and intravenous administration of a single dose (10 μg) of sufentanil during labor, using a combined spinal–epidural technique.

Materials and Methods

Twenty-four ASA physical status 1 or 2 parturients requesting epidural analgesia during active labor were enrolled in the study. All patients were at term and had uncomplicated pregnancies and normal fetal heart tracings. All gave written informed consent to an institutionally approved human research protocol. When patients first requested analgesic medication, the following combined spinal–epidural technique was used. The patient was placed in the right or left lateral decubitus and the usual aseptic preparation and draping performed. A 4½-inch 17-G Weiss needle was inserted into the epidural space at either the L2–L3 or L3–L4 interspace using the loss of resistance to air technique. A $4^{1}/_{16}$-inch 25-G Whitacre spinal needle (Becton-Dickenson, Rutherford, NJ) was passed *via* the epidural needle into the subarachnoid space until clear cerebrospinal fluid (CSF) was obtained.

All patients then received, in a randomized, double-blind fashion, an intrathecal (2 ml), intravenous (2 ml), and epidural (10 ml) injection at roughly the same time. One of the injectates contained 10 μg sufentanil; the other two contained only saline. (The epidural injection was given *via* the epidural needle immediately after removal of the spinal needle. After the epidural and spinal injections, an epidural catheter was placed 2 cm into the epidural space, but no local anesthetics were injected.) All injectates were prepared by an anesthesiologist not involved in subsequent data collection and were randomized according to a random number scheme with instructions contained in sequentially numbered, opaque envelopes.

Analgesia was assessed using a 10-cm linear visual analogue scale at the time of study drug injection and 10, 20, 30, 40, 60, 90, 120, and 180 min thereafter. Maternal

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blood pressure was measured at the same intervals. Patients could request additional analgesia (bupivacaine 0.25% *via* the epidural catheter) if pain relief was unsatisfactory by 15 min after injection of study drug. When additional analgesia was requested, the study protocol and data collection were terminated, and patients then were given epidural bupivacaine as per usual clinical routine for the remainder of their labor. The time from study drug administration until a request for additional analgesia was noted. Side effects (pruritus, nausea, and somnolence) were assessed using a four-point ordinal scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Continuous electronic fetal heart rate monitoring was used for all patients throughout labor.

Continuous ordinal data were analyzed using Kruskal-Wallis analysis of variance and Mann-Whitney tests. Data are expressed as median and interquartile range (25–75% confidence interval). A value of $P < 0.025$ was considered to indicate statistical significance.

Results

Demographic characteristics did not differ among groups (table 1). The median duration until first request for additional analgesia (fig. 1) was 84 (70–92) min in the intrathecal group (n = 9), 30 (23–32) min in the intravenous group (n = 7), and 24 (17–30) min in the epidural group (n = 8) ($P < 0.001$). Baseline visual analogue scale scores were equivalent for all groups. The intrathecal group showed rapid (within 10 min) and significant decrease in visual analogue scale scores (fig. 2). Visual analogue scale scores in the intravenous and epidural groups did not decrease at any observation point and remained greater than those in the intrathecal group (fig. 2).

No patient complained of dysphoria, excessive sedation, or nausea or demonstrated abnormalities of fetal heart rate tracing. No patient developed hypotension or evidence of motor blockade. Three patients in the intrathecal group complained of pruritus (two moderate and one severe). None required treatment for pruritus. No patient developed post–dural puncture headache.

TABLE 1. Maternal Demographic Characteristics

Characteristic	Intrathecal (n = 9)	Epidural (n = 8)	Intravenous (n = 7)
Age	29 ± 6	29 ± 4	31 ± 3
Height (cm)	172 ± 2	170 ± 2	170 ± 1
Weight (kg)	75 ± 9	84 ± 12	77 ± 9
Parity			
0	6	3	5
≥1	3	5	2
Birth weight (kg)	3.8 ± .4	3.6 ± .4	3.5 ± .4
Cervical dilatation at time of study drug administration (cm)	4.6 ± 1.6	4.3 ± .5	3.8 ± .8

Data expressed as means ± SD.
No significant difference among groups.

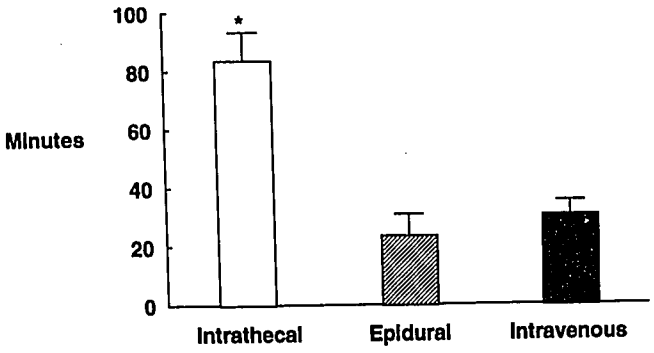

FIG. 1. Duration of analgesia (median, interquartile range) after sufentanil administration. *$P < .001$, intrathecal *versus* epidural and intravenous.

Discussion

The principal finding of this study is that sufentanil 10 μg administered intrathecally provided effective analgesia of 1–2-h duration during labor, whereas the same dose given intravenously or epidurally failed to provide satisfactory pain relief. Although the number of patients in this study was small, the differences in quality and duration of analgesia between the intrathecal and the other two groups were striking and highly significant. We had originally planned to enroll more patients in this protocol but terminated the study when it became clear that a large number of the subjects had clearly unsatisfactory analgesia. Data analysis upon termination of the study confirmed that the unsatisfactory analgesia was confined to the epidural and intravenous groups. Although the incidence of side effects was low, the small study size precludes any definitive statement about side effects of this technique in a larger population.

A number of recent studies have suggested that the analgesic effects of epidural and intravenous administration of various lipid-soluble opioids (fentanyl, alfentanil, butorphanol, and meperidine) are largely equivalent.[2–8] However, these studies did not assess intrathecal compared to parenteral administration of these agents. Our findings support other recent reports that intrathecal opioids,[11] in particular sufentanil,[9,10] provide effective analgesia during labor. We propose that low-dose intrathecal sufentanil has a primarily intraspinal, rather than systemic, site of action. Additional studies measuring both plasma and CSF concentrations of sufentanil after administration by these routes are needed to substantiate this finding further. Although our study suggests increased potency of sufentanil after intrathecal administration, the lack of a dose–response study design precludes

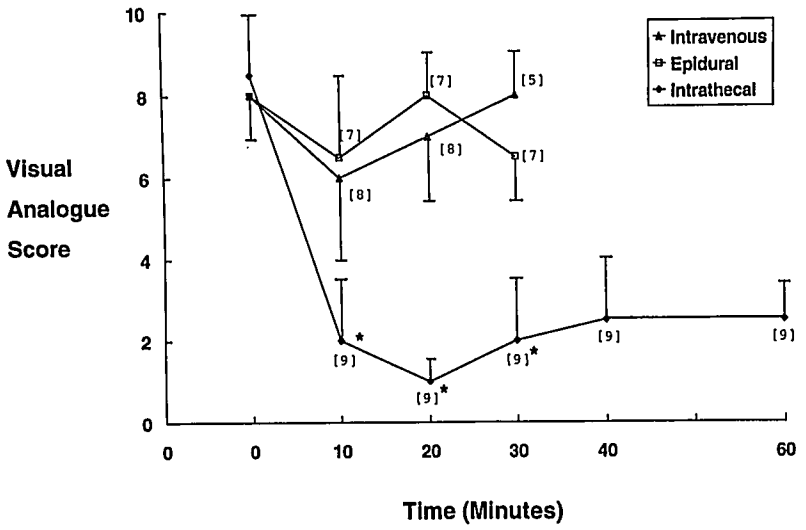

FIG. 2. Visual analog scale scores (median, interquartile range) after sufentanil administration. Insufficient numbers of patients precluded data tabulation after 30 min in the intravenous and epidural groups. Numbers in brackets indicate number of patients in each group at the time of assessment. *$P < .001$, intrathecal *versus* intravenous and epidural. *$P < .001$ *versus* intrathecal baseline visual analog scale score.

any estimation of relative potency ratios by the various routes.

Two previous studies have compared epidural to intravenous sufentanil in human clinical trials. Cohen *et al.* found that post–cesarean delivery analgesia after administration of epidural sufentanil 30 μg was twice as long (200 *vs.* 108 min) as that after the same dose of intravenous sufentanil, although this difference was not statistically significant because of low numbers of patients (n = 6 in each group) in that study.[6] Rossell *et al.* studied intra- and postoperative effects of sufentanil 0.7 $\mu g \cdot kg^{-1}$ either intravenously or epidurally in thoracic surgery patients.[12] They concluded that the epidural route provided longer and more profound analgesia.

One of the alleged advantages of neuraxial, as opposed to parenteral, administration of opioids is the ability to provide analgesia with small doses of drug. However, it appears that as lipid solubility increases, the differential between effective epidural and parenteral doses narrows.[13] Moreover, many of the studies using epidural sufentanil have used doses quite larger than would be considered appropriate for intravenous administration. For example, several investigators have used epidural sufentanil at a dose of 50 μg or greater in awake patients during labor or cesarean delivery.[6,14,15] It is unlikely that 50 μg intravenous sufentanil would be well tolerated in awake patients. Therefore, although epidural sufentanil may provide effective analgesia, large doses are required. These doses, if unintentionally injected intravenously, would likely result in profound respiratory depression. Lower doses (5–10 μg) of epidural sufentanil may provide effective analgesia but only when combined with local anesthetic supplementation.[15] Epidural sufentanil alone appears to provide insufficient analgesia during labor.[16]

The quality of analgesia after administration of intrathecal sufentanil was excellent; however, all patients required some subsequent epidural local anesthetic supplementation. The rapid onset and relatively short duration of sufentanil analgesia can be explained by pharmacokinetic data.[17,18] Previous investigations have found that sufentanil has a high affinity for μ-opioid receptors. However, the clearance from CSF was found to be rapid, with a mean residence time in CSF of 0.92 h.[17] Moreover, the unsatisfactory analgesia in the epidural group is likely explained by the increased potency of intrathecal *versus* epidural sufentanil. CSF concentrations of sufentanil after a bolus dose of 75 μg given epidurally are similar to these after only 15 μg given intrathecally.[17]

A concern regarding the use of intrathecal medications in humans is potential neurotoxicity. A recent study by Rawal *et al.* in sheep demonstrated histologic changes consistent with neurotoxicity after intrathecal administration of 7.5 μg/kg sufentanil repeated every 6 h for 72 h.[19] Smaller doses (0.75 μg/kg) resulted in only mild changes. The clinical relevance of these findings after such large doses of sufentanil is unclear. Moreover, the experimental model (sheep) has a very small intrathecal space in contrast to that of humans. Thus, acute dilution of drug within the CSF and rapid clearance from CSF is likely to be much greater in humans than in the experimental model used by Rawal *et al.* None of the existing reports in the literature describes any neurologic deficits after administration of either epidural or intrathecal sufentanil.

We chose our dose of sufentanil (10 μg) because it is comparable to the dose in preliminary reports using intrathecal sufentanil as a sole agent for labor analgesia. Moreover, we did not feel comfortable giving a dose larger than 10 μg intravenously to awake patients during labor. The absence of motor blockade or hypotension suggest

that this technique may be a useful adjunct to the initiation of obstetric epidural analgesia. We conclude that 10 μg intrathecal sufentanil provides rapid and profound analgesia during labor. Further studies are warranted to assess the effect of this technique on subsequent epidural local anesthetic requirements or on the progression of labor.

References

1. Datta S: Relief of labor pain by regional anesthesia, The Obstetric Anesthesia Handbook. Edited by Datta S. Boston, Mosby Yearbook, 1992, pp 115–148
2. Camann WR, Loferski BL, Fanciullo GJ, Stone ML, Datta S: Does epidural administration of butorphanol offer any clinical advantage over the intravenous route? ANESTHESIOLOGY 76:216–220, 1992
3. Loper KA, Ready LB, Downey M, Sandler AN, Nessly M, Rapp S, Badner N: Epidural and intravenous fentanyl infusion are clinically equivalent after knee surgery. Anesth Analg 70:72–75, 1990
4. Ellis DJ, Millar WL, Reisner LS: A randomized double-blind comparison of epidural *versus* intravenous fentanyl infusion for analgesia after cesarean section. ANESTHESIOLOGY 72:981–986, 1990
5. Colpaert FC, Leysen JE, Michiels M, Vanden Hoogen RH: Epidural and intravenous sufentanil in the rat: Analgesia, opiate receptor binding and drug concentrations in plasma and brain. ANESTHESIOLOGY 65:41–49, 1986
6. Cohen SE, Tan S, White PF: Sufentanil analgesia following cesarean section: Epidural versus intravenous administration. ANESTHESIOLOGY 68:129–134, 1988
7. Perriss BW, Latham BV, Wilson IH: Analgesia following extradural and IM pethidine in post-cesarean section patients. Br J Anaesth 64:355–357, 1990
8. Camu F, Debucquoy F: Alfentanil infusion for postoperative pain: A comparison of epidural and intravenous routes. ANESTHESIOLOGY 75:171–178, 1991
9. Naulty JS, Barnes D, Becker R, Pate A: Continuous subarachnoid sufentanil for labor analgesia (abstract). ANESTHESIOLOGY 73: A964, 1990
10. Honet JE, Arkoosh VA, Huffnagle HJ, Norris MC, Leighton BL: Comparison of fentanyl, meperidine, and sufentanil for labor analgesia (abstract). ANESTHESIOLOGY 75:A839, 1991
11. Leighton BL, DeSimone CA, Norris MC, Ben-David B: Intrathecal narcotics for labor revisited: The combination of fentanyl and morphine intrathecally provides profound, prolonged analgesia. Anesth Analg 69:122–125, 1989
12. Rossell MJ, VanDenBroek M, Boer EC, Prakash O: Epidural sufentanil for intra- and postoperative analgesia in thoracic surgery: A comparative study with intravenous sufentanil. Acta Anaesthesiol Scand 32:193–198, 1988
13. McQuay HJ, Sullivan AF, Smallman K, Dickenson AH: Intrathecal opioids, potency, and lipophilicity. Pain 36:111–115, 1989
14. Celleno D, Capogna G, Sebastiani M, Costantino P, Muratori F, Cipriani G, Emanuelli M: Epidural analgesia during and after cesarean delivery: Comparison of five opioids. Reg Anesth 16: 79–83, 1991
15. Steinberg RB, Powell G, Hu X, Dunn SM: Epidural sufentanil for analgesia for labor and delivery. Reg Anesth 14:225–228, 1989
16. Steinberg RB, Dunn SM, Dixon DE, Rehm KL, Pastides H, Hu X: Comparison of sufentanil, bupivacaine, and their combination for epidural analgesia in obstetrics. Reg Anesth 17:131–138, 1992
17. Hansdottir V, Hedner T, Woestenborghs R, Nordberg G: The CSF and plasma pharmacokinetics of sufentanil after intrathecal administration. ANESTHESIOLOGY 74:264–269, 1991
18. Ionescu IT, Taverne RHT, Hovweling PL, Drast RH, Nuijten S, VanRossum J: Pharmacokinetic study of extradural and intrathecal sufentanil anesthesia for major surgery. Br J Anaesth 66:458–464, 1991
19. Rawal N, Nuutinen L, Raj P, Lovering SL, Gobuty AH, Hargardine J, Lehmukuhl L, Herva R, Abouleish E: Behavioral and histopathologic effects following intrathecal administration of butorphanol, sufentanil and nalbuphine in sheep. ANESTHESIOLOGY 75:1025–1034, 1991