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Double-blind Comparison of Morphine and Bupivacaine for Continuous Epidural Analgesia in Labor

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In a double-blind, randomized study 16 healthy parturients received epidural morphine, 0.025 per cent, or bupivacaine, 0.25 per cent, for continuous lumbar epidural analgesia in active labor. Morphine was dissolved in dextrose to avoid possible inhibition by saline of agonist-receptor binding. Adequacy of analgesia was assessed using a simple pain relief score and by observing maternal blood pressure, pulse rate, and response to pin scratch. Skin temperature was measured to identify sympathetic blockade. Neonatal status was determined by Apgar scores, umbilical cord blood gas values, and neurobehavioral assessment at 2–4 and 20–26 hours postpartum. Bupivacaine provided pain relief in all 8 subjects, while morphine produced acceptable relief in only 2 subjects given 2.5 mg and 3.5 mg, respectively ($P < 0.05$). Six parturients having unsatisfactory analgesia with morphine later achieved good pain relief with 2-chloroprocaine, 2 per cent. Blood pressure decreased 5 min after bupivacaine ($P < 0.05$) but not after morphine. Changes in blood pressure were transient, with no patient requiring vasopressor therapy. Skin temperature increased after bupivacaine ($P < 0.05$) but not after morphine. Numbness to pin scratch was demonstrated in both morphine subjects with pain relief and in all bupivacaine subjects. Apgar scores and umbilical cord blood gas values were similar in both groups. Borderline status in the Scanlon neurobehavioral examination occurred in 6 neonates in the morphine group at the first assessment while all bupivacaine neonates were normal ($P < 0.05$). When 2-chloroprocaine was given after morphine, its mean duration of action was increased from a normal value of 40–65 min to 83 ± 5.5 min. Thus, morphine in dextrose, in the low doses employed, is unsuitable for continuous epidural analgesia in labor. Insufficient occupancy of opiate receptors by morphine provides a likely explanation of these findings. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Anesthetics, local: bupivacaine. Analgesics: morphine.)

SEVERAL OPIATE RECEPTOR SITES are located in substantia gelatinosa in the dorsal horn grey matter of spinal cord. Yaksh and Rudy[1] demonstrated a pharmacologically specific spinal effect of intrathecal narcotics in animals, suggesting direct modulation of substantia gelatinosa activity.

The report of Behar *et al.*[2] describing successful use of small doses of epidural morphine in acute and chronic pain suggested a spinal effect. Their inability to demonstrate sympathetic or motor blockade led us to study morphine for continuous lumbar epidural analgesia (LEA) in labor since these characteristics would confer advantages over currently used local anesthetics.

Because *in vitro* animal studies[3] suggest that sodium inhibits opiate agonist-receptor interaction, we dissolved morphine in dextrose and compared it with bupivacaine in a double-blind study of parturients having LEA.

Methods

We studied sixteen parturients, free of maternal or pregnancy associated disease, who requested epidural analgesia for normal labor with a healthy singleton fetus in cephalic presentation. The Clinical Research Practices Committee approved the protocol, and each subject gave informed consent.

Morphine sulfate, 1 mg/ml, was prepared by diluting 15 mg with 5 per cent dextrose. We further diluted 2.5 mg aliquots of this mixture with 5 per cent dextrose, 7.5 ml, yielding 10 ml of solution containing 0.25 mg/ml. Bupivacaine, 0.25 per cent, was prepared in 10-ml aliquots to permit blinding of investigator and subject to drug identity. Random selection determined the choice of drug.

Immediately before establishing LEA, we recorded control values of maternal blood pressure (Riva-Rocci method), pulse rate, and anterior thigh skin temperature. Fetal heart rate and uterine activity were evaluated electronically§ for at least 10 min prior to initiating epidural analgesia and throughout the remainder of labor.

Following an intravenous (iv) pre-load of 500 ml of balanced salt solution, we instituted LEA during the active phase of labor.[4] We identified the epidural space by means of loss of resistance to air and advanced the epidural cannula 3–5 cm via an 18-gauge Hustead needle. The study drug was injected through

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§ Corometrics Fetal Monitor 101B—Corometrics Medical Systems, Inc., North Haven, Conn.

TABLE 1. Pain Relief Scoring System

	Pain Score
Pain or Pressure Unaffected	1
Significant Pain or Pressure + +	2
Slight Pain or Pressure +	3
No Pain: Some Pressure	4
No Pain: No Pressure	5

a 0.22 μ Millex® Filter¶ in an initial dose of morphine, 2 mg, or bupivacaine, 20 mg, with the subject in the left semi-lateral position. Blood pressure, pulse rate, and skin temperature were observed, and pain relief was scored on a 1–5 scale at 3, 5, and 10 min after injection (table 1).

A pain relief score of 3 or less after 10 min indicated inadequate relief and up to three additional increments of morphine, 0.5 mg, or bupivacaine, 5 mg, were given at 10-min intervals to achieve acceptable analgesia (total morphine, 3.5 mg, or bupivacaine, 35 mg). When pain relief failed, we substituted 2-chloroprocaine (2 per cent, 160–200 mg) for the study drug. The maximum period of inadequate pain relief permitted was 40 min.

When the test solution provided relief, we observed pulse, blood pressure, pain relief score, and skin temperature at 15, 20, 30, 60, 90, and 120 min and recorded dermatome levels at 30 and 60 min. We gave additional doses of morphine, 2 mg, or bupivacaine, 20 mg (plus increments when required), throughout labor and repeated the observations.

Parturients who continued to have adequate pain relief from morphine or bupivacaine received morphine, 3.75 mg, or bupivacaine, 37.5 mg, in the sitting position to provide perineal analgesia for delivery. The need for supplemental pudendal block or infiltration analgesia was recorded.

We assessed neonatal status by umbilical cord blood gases, 1- and 5-min Apgar scores, and the Scanlon neurobehavioral examination[5] at 2–6 and 20–26 hours after delivery. We designated infants sleepy if more than three S2 states occurred during examination, and irritable with more than three A4 states, all other infants being normal. In the specific tests,[5] we considered scores of 0 or 1, abnormal, and 2 or 3, normal. The last item of the neurobehavioral examination (General Assessment) requires the examiner's appraisal of the infants' performance on the entire examination.[5] Infants who demonstrated abnormal responses in two or more major categories, *e.g.*, alertness, tone, reflex activity were judged to perform poorly in the examination and were assigned a borderline status.

Data were analyzed with 2-tailed Student's test and Fisher's exact test; significance was assumed when $P < 0.05$.

Results

Subjects in both groups were similar before LEA (table 2). In early labor 6 parturients in each group received meperidine and/or a tranquilizer with no significant dose difference between groups.

Following morphine, satisfactory analgesia was obtained in two patients (table 3). One subject demonstrated a pain relief score of 4 after receiving 2.5 mg. Good labor analgesia resulted from an additional 2 mg given 115 min later, but a 3.75-mg delivery dose failed to produce analgesia for episiotomy. Another morphine patient required 3.5 mg to attain pain relief, which lasted only 15 min. Later, she received 2.5- and 2-mg doses before proceeding to cesarean section with 2-chloroprocaine (3 per cent) for failure to progress in labor. Morphine failed to produce analgesia in six subjects receiving a mean dose of 3.25 mg. In contrast, all eight bupivacaine subjects obtained satisfactory analgesia, five from the initial 20-mg dose, two after 25 mg, and one following 30 mg (table 3). This difference in analgesia between groups was significant. In the six morphine subjects later given 2-chloroprocaine (initial dose, 160–200 mg) the mean duration of analgesia (83 ± 5.5 min) was longer than the expected duration of 40–65 min.[6]

Following bupivacaine, skin temperature increased from 33.3 ± 0.3° C to 33.7 ± 0.2° C ($P < 0.05$) within

TABLE 2. Comparison of Subjects

	Morphine (n = 8)	Bupivacaine (n = 8)
Age (Yr)	23 ± 1.8	27 ± 1.9
Gravida		
1	4	5
>1	4	3
Cervical Dilation (cm)	4 ± 0.5	5 ± 0.5
Control Parameters		
Pulse	92 ± 4.7	90 ± 2.8
Skin Temp (°C)	32.9 ± 1.5	33.3 ± 0.3
Systolic BP (torr)	116 ± 5.8	122 ± 6.1
Diastolic BP (torr)	47 ± 16.0	75 ± 5.3

These values are mean ± SEM. There were no significant differences between groups.

¶ Millipore Corporation, Bedford, Ma. 01730.

3 min and remained significantly elevated 60 min after injection. Morphine caused no significant temperature change.

Numbness to pin scratch was observed in the two morphine subjects with pain relief. Thirty min after morphine, 2.5 mg, one subject had hypalgesia from T11 to L1 while the other developed a band of analgesia from L1 to L5 following 3.5 mg. Thirty min after a subsequent 2-mg dose, the former parturient reached a maximum spread from T8 to L1. No further extension of dermatome levels occurred in the latter subject. Morphine did not produce motor block. Numbness to pin scratch but no significant motor block occurred in all bupivacaine parturients. When receiving morphine two mothers felt drowsy, while one became euphoric after a cumulative dose of 5.5 mg. No subject complained of nausea or itching, and we observed no clinical signs of respiratory depression.

We observed no clinically significant fetal heart decelerations in morphine or bupivacaine subjects. A comparable incidence of low baseline (beat to beat) variability (<10 beats/min) occurred in both groups. Uterine activity monitoring revealed no obvious abnormality following either drug.

There was no significant difference in requirements for supplemental pudendal or infiltration anesthesia.

Three bupivacaine and one morphine subject later received 2-chloroprocaine (3 per cent) for cesarean section, indications for which were unrelated to epidural block. The 25 per cent overall cesearean section rate exceeds the normal 15–20 per cent for our high-risk referral unit.

Neonatal status as reflected by Apgar scores and umbilical cord blood gas values was similar in both groups (table 4). Neonatal neurobehavioral examination at 2–6 hours postpartum revealed borderline status in six infants from the morphine group while all babies of the bupivacaine group were normal ($P < 0.05$). We found no significant difference in General Assessment at 20–26 hours. Other neurobehavioral variables (alertness, reflex activity, tone, response decrement) were not significantly different between groups at either examination.

TABLE 3. Incidence of Pain Relief (Pain Relief Score > 3) after Initial (8 ml) or Incremental (2 ml) Doses of Epidural Morphine or Bupivacaine in Labor

	Pain Relief				
	After Initial Dose	After Initial Dose Plus 1 Increment	After Initial Dose Plus 2 Increments	After Initial Dose Plus 3 Increments	No Pain Relief
Morphine (n = 8)	0	1	0	1	6
Bupivacaine (n = 8)	5*	2	1	0	0*

* $P < 0.05$. Bupivacaine *vs.* morphine groups.

Discussion

In this study bupivacaine proved superior to morphine for epidural analgesia during labor. We selected small doses of morphine to decrease the possibility of pain relief being achieved by systemically effective blood levels, which might cause neonatal depression.

Our morphine dosage compares with that shown to be effective in various types of acute and chronic pain[2,7,8] and in postoperative pain.[9] The work of Yaksh and Rudy[1] in animals and Wang *et al.*[10] in patients with cancer pain demonstrates the effectiveness of intrathecal morphine, suggesting that in cerebrospinal fluid (CSF) morphine gains access to spinal cord opiate receptors.

After epidural injection of meperidine (100 mg in normal saline), Cousins *et al.*[11] correlated the onset of analgesia in 15 min with CSF meperidine levels of 0.5–2 mg/l. Complete pain relief, in 12 to 20 min, was associated with levels of 10–20 mg/l. Their data suggested an initial analgesic effect of meperidine by a spinal cord action, although later analgesia might have been due in part to "blood borne" effects.

TABLE 4. Immediate Neonatal Status

	Mean Values Cord Blood Gases					
	*p*H		P_{O_2} (torr)		P_{CO_2} (torr)	
	V	A	V	A	V	A
Morphine	7.36 ± 0.01	7.25 ± 0.02	27.5 ± 2.3	13 ± 0.8	43 ± 1.8	57 ± 3.0
Bupivacaine	7.31 ± 0.02	7.22 ± 0.03	28.0 ± 2.0	14 ± 1.8	42 ± 2.4	52 ± 3.8

These values are mean ± SEM. There were no significant differences between groups.

Our disappointing results with labor pain confirm those of Husemeyer *et al.*[12] using 2 mg morphine in saline. Magora *et al.*[7] achieved good pain relief in 10 of 16 patients after induced abortion and fair relief in only 2 of 14 patients in labor at term.

Snyder[3] found that *in vitro* affinity of opiate receptors in guinea pig ileum depends on sodium state of the receptor. In the presence of sodium, opiate antagonist receptors increase in number, agonist receptors decrease, and pure opiate agonist drugs become 12–60 times weaker. Behar *et al.*[2] diluted morphine in saline or dextrose. Magora[7] prepared morphine HCl in 10 per cent dextrose, subsequently diluted with saline for administration. Other investigators have diluted morphine in 0.9 per cent saline.[8,9] To avoid any potentially detrimental effects of sodium, we diluted morphine sulfate in 5 per cent dextrose. However, this conferred no advantage in labor, suggesting the sodium content of the diluent was unimportant. Reports which demonstrate the analgesic effectiveness of morphine diluted in dextrose or saline, in other types of pain, would suggest that, *in vivo*, spinal cord opiate receptors in humans are less susceptible to sodium inhibition than guinea pig ileal receptors *in vitro*.

The presence of distended epidural veins at term is well recognized, and we support the suggestion of Husemeyer *et al.*[12] that increased vascularity of the epidural space may be responsible for rapid clearance of epidural morphine, leaving ineffective concentrations to enter CSF. By increasing dosage we could overcome loss of drug by vascular absorption, but this would carry the risk of undesirable systemic effects. The addition of epinephrine might possibly diminish vascular absorption of morphine. Booker *et al.*[13] recently reported increased efficacy of epidural morphine following pretreatment with saline containing epinephrine. Adequate analgesia might have developed if we had waited longer for the morphine to work. Epidural morphine can be slow in onset, producing adequate analgesia after more than 40 min, but a delay of this magnitude to relieve labor pain is unacceptable in a clinical setting.

The pain of first stage labor can be obliterated by sympathetic nerve block. The failure of epidural morphine to interrupt sympathetic pathways by its spinal effect, was reported by Behar *et al.*[2] The absence of temperature change in our subjects confirms the lack of sympathectomy and may explain the limited efficacy of epidural morphine in obstetric pain.

Leslie *et al.*[14] reported segmental hypalgesia to pin scratch after epidural dilaudid 0.5 mg (≃meperidine 30 mg) and ascribed it to a spinal nociceptive effect. Although any site of action between Laminae I and VI might explain this,[15] morphine is known to suppress thermal nociceptive Lamina V responses in experimental cats.[16] Our finding of a narrow hypalgesia band, increasing after a cumulative dose of morphine, 4.5 mg, emphasizes the need to look for changed modality. Although we demonstrated impaired perception only in mothers having pain relief, its distribution in our second subject did not accord with obstetric analgesia underlining the unreliability of this assessment.

Magora *et al.*[7] noted that epidural injection of bupivacaine given after morphine relieved pain for up to 6 hours. In our study, the administration of 2-chloroprocaine after epidural morphine produced a prolonged duration of action for this local anesthetic, perhaps representing potentiation of chloroprocaine's anesthetic effect.

Our neurobehavioral data might be criticized because seven morphine and three bupivacaine subjects later received 2-chloroprocaine. However 2-chloroprocaine should not have influenced neonatal outcome since it does not compromise neurobehavioral scores.[17] We cannot explain the borderline status of the morphine neonates at 2–6 hours postpartum although it is unlikely to be a drug effect since one of the two normal babies was born to the mother receiving the largest dose of morphine. While neurobehavioral assessment has greater sensitivity than Apgar scores, these statistically significant findings may have little clinical importance, since assignment to a borderline or normal category is often subjective and open to observer bias.

We conclude that, in the doses employed, morphine in dextrose is unsuitable for continuous lumbar epidural analgesia in labor. Insufficient occupancy of opiate receptors by morphine provides a likely explanation for our findings. The possible synergism between epidural morphine and local anesthetics is an interesting finding which merits further investigation.

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