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Labor Analgesia with Epidural Bupivacaine Plus Fentanyl: Enhancement with Epinephrine and Inhibition with 2-Chloroprocaine

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Epidural injection of drug combinations may decrease toxicity by decreasing the dose of each component, but may also result in detrimental drug interactions. In this study interactions among bupivacaine, fentanyl, epinephrine, 2-chloroprocaine, and lidocaine for epidural analgesia during labor were examined. In part 1 of the study, healthy parturients received in a random manner either 10 ml of 0.25% bupivacaine with 5 μg/ml fentanyl (n = 50), or 10 ml of this combination with 3.33 μg/ml freshly added epinephrine (n = 50). Epinephrine prolonged the median duration of pain relief (180 *vs.* 138 min, $P < 0.05$) without affecting duration of first or second stages of labor, or neonatal Apgar scores. Blood pressure decreased slightly more in those receiving epinephrine, although the incidence of hypotension requiring treatment did not differ between groups. Part 2 of the study evaluated the possibility that local anesthetic used for confirming catheter tip location may interfere with the analgesic action of this bupivacaine-fentanyl-epinephrine (BFE) combination. In 50 additional parturients, a test dose of either 2-chloroprocaine (n = 25) or lidocaine (n = 25) was injected through the epidural catheter and was followed by injection of the BFE mixture. The lidocaine test dose group had a greater duration of analgesia than the 2-chloroprocaine test dose group (median duration of 164 *vs.* 91 min, $P < 0.05$). The authors conclude that the addition of epinephrine 3.33 μg/ml significantly increases the duration of analgesia obtained from 0.25% bupivacaine with 5 μg/ml fentanyl. However, prior injection of 2-chloroprocaine, but not lidocaine, significantly decreases the duration of analgesia achieved with this BFE mixture. (Key words: Analgesics, opioid: fentanyl. Anesthesia: obstetric. Anesthetic techniques: epidural. Sympathetic nervous system, catecholamines: epinephrine.)

ALTHOUGH EPIDURALLY ADMINISTERED bupivacaine has many desirable qualities for analgesia during labor (minimal motor blockade, minimal fetal effects), its onset for pain relief is slow and its relatively brief duration necessitates repeated injections or continuous infusion for labor analgesia. Fentanyl hastens onset, enhances analgesia, and prolongs the duration of analgesia provided by epidurally administered bupivacaine during labor,[1] although these moderate effects have not always reached statistical significance.[2] Epinephrine similarly enhances analgesia provided by epidurally administered bupivacaine.[3] Part 1 of this study examines the hemodynamic and analgesic effects of epinephrine on a bupivacaine-fentanyl combination.

The long-lasting analgesia that might be provided by the epidural administration of a bupivacaine-fentanyl-epinephrine mixture would be a significant advantage on a busy labor service. However, this epinephrine-containing mixture may not safely and reliably identify iv catheter placement.[4] Injection of 2-chloroprocaine or lidocaine effectively identifies iv catheter placement in unpremedicated volunteers.[5,6] However, there is reason for concern that 2-chloroprocaine may interfere with the potency of subsequently administered anesthetic solutions.‡ Although epidurally administered 2-chloroprocaine, in doses necessary for cesarean section, interferes with the action of epidurally administered fentanyl,[7] the effect of smaller doses, as used to confirm location of catheter tip, has not been examined. The second part of this study evaluates the effect of using 2-chloroprocaine or lidocaine to confirm location of the catheter tip on the analgesic duration of a bupivacaine-fentanyl-epinephrine mixture during labor.

Materials and Methods

Following approval by the Clinical Research Practices Committee and after obtaining informed consent, 121 ASA physical status 1 or 2 laboring parturients participated in part 1 of the study. All women were in active labor and with cervical dilation < 7 cm at the time they requested epidural analgesia. After subcutaneous infiltration with 1% lidocaine, the tip of a #16 Hythe needle was inserted into the epidural space at the L2-3, L3-4, or L4-5 interspace using the loss or resistance technique with air or a small amount (<3 ml) of saline. A single distal port Portex™ (Burron Medical Inc., Bethlehem, PA) catheter was inserted no more than 3 cm beyond the tip of the needle. Patients were then positioned supine with left lateral tilt.

Before local anesthetic injection each woman rated her level of pain during uterine contractions on a ten-point verbal scale (1 = no pain, 10 = worst pain ever experi-

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‡ Hodgkinson R, Husain FJ, Bluhm C: Reduced effectiveness of bupivacaine 0.5% to relieve labor pain after prior injection of chloroprocaine 2% (abstract). ANESTHESIOLOGY 57:A201, 1981.

enced). Participants then received in a random manner 10 ml of solution containing either 0.25% bupivacaine with fentanyl 5 μg/ml, or this combination with freshly added epinephrine 3.33 μg/ml. The nurse and patient were blinded to the drug mixture administered. Local anesthetic solution was injected in increments: 2 ml, followed in 5 min by 5 ml, followed in 2 min by 3 ml. For study purposes, the 3 ml injection was considered time 0. If pain relief was inadequate by patient report 21 min after the 3 ml injection, or if the most cephalad sensory level was below T10, the patient received an additional 5 ml of the original local anesthetic solution. If pain relief was inadequate 15 min after this injection, or if delivery occurred within 60 min of local anesthetic solution injection, the patient was dropped from the study.

Parturients assessed the adequacy of their pain relief on a four-point scale (1 = none, 2 = a little, 3 = a lot, 4 = complete) every 3 min for 18 min, beginning 3 min after the 3-ml injection. Following the last assessment, the most cephalad level of sensory analgesia to pin testing was recorded. Onset of analgesia was defined as time from the 3 ml injection until the patient reported a pain relief of 3 or 4. Duration of analgesia was defined as time from the 3 ml injection until the nurse or patient first requested a reinforcing dose of local anesthetic, or, if no additional doses were required, at delivery.

Maternal blood pressure and heart rate were measured using a Dinamap™ vital signs monitor before injection, every minute for 5 min after the 5-ml injection, then every 3 min for 18 min. Hypotension was defined as a decrease in systolic blood pressure by 30% from the initial blood pressure measurement in the study or to a value below 100 mmHg. Hypotension was treated by increasing the rate of iv fluid administration and, if necessary, administering ephedrine. Maternal age, height, weight, parity, duration of first and second stage of delivery, mode of delivery, and 1 and 5 min Apgar scores were also recorded.

An additional 62 parturients participated in the second part of the study. Following approval of the Clinical Research Practices Committee and after informed consent was obtained, a lumbar epidural catheter was inserted as described as above. Participants then received in a random manner either 2% 2-chloroprocaine or 2% lidocaine for test dosing. Test doses consisted of a 2-ml injection to evaluate possible subarachnoid injection, followed in 5 min by a 5-ml injection to evaluate possible iv injection. Two minutes later, 10 ml of 0.25% bupivacaine with freshly added fentanyl (5 μg/ml) and epinephrine (3.33 μg/ml) were incrementally injected. For study purposes, the start of the 10-ml injection was considered to be time 0. Monitoring and data acquisition were identical to the first part of the study.

Unless otherwise stated, data are presented as means ± SEM. Although the two parts of the study were very similar in design, they were analyzed separately. Within each part, the two treatment groups were compared for maternal demographic data, labor data, level of sensory analgesia, and, in patients receiving a redose, duration of analgesia using a Student's t test. The level of sensory analgesia was also compared using the Kolmogorov-Smirnov frequency test. Noncontinuous labor and demographic data were compared using the Fisher-Yates exact probability test. Blood pressure and heart rate data during uterine contractions and after ephedrine administration were eliminated, and the remaining hemodynamic data compared between groups using a repeated measures multivariate analysis of variance, and within groups, using a repeated measures one-way analysis of variance. Significant group differences by these analyses were followed by multiple comparisons using the Holm's modified Bonferroni adjustment. Onset and duration of analgesia in all patients were compared by the Kaplan-Meier method followed by the logrank test. $P < 0.05$ was considered significant.

Results

Part 1: Effect of Epinephrine

One hundred women provided data for analysis. The groups did not differ in demographic or labor data (table 1). All cesarean sections were performed because of cephalopelvic disproportion, failure to progress, or fetal stress. Only one neonate had a 1-min Apgar score of less than 7.

The groups did not differ in baseline pain score (mean of 7.7 in bupivacaine/fentanyl group, 7.4 in added epinephrine group). Although the groups did not differ in cephalad spread of sensory analgesia achieved after injection of 10 ml of solution, the addition of epinephrine significantly prolonged analgesia (table 2; fig. 1, upper

TABLE 1. Labor and Demographic Data: Study Part 1

Parameter	0.25% Bupivacaine + fentanyl (n = 50)	0.25% Bupivacaine + fentanyl + epinephrine (n = 50)
Age	23 ± 0.9	24 ± 1.1
Height (cm)	158 ± 5	157 ± 5
Weight (kg)	70 ± 2.5	72 ± 2.8
Nullipara	30 (60%)	30 (60%)
First stage (min)	566 ± 47	485 ± 35
Second stage (min)	81 ± 13	71 ± 9
Cesarean section	10 (20%)	8 (16%)

No significant differences.

TABLE 2. Analgesia after Epidural Injection

Parameter	0.25% Bupivacaine + fentanyl (n = 50)	0.25% Bupivacaine + fentanyl + epinephrine (n = 50)
Most cephalad sensory dermatome (thoracic)		
Right	9 ± 0.4 (10)*	8 ± 0.4 (9)*
Left	9 ± 0.4 (10)*	8 ± 0.4 (9)*
Analgesia onset (min)	6.5 ± 0.7	4.9 ± 0.5
Analgesia duration (min)*	138	180†
Patients requiring 15 ml	19	14

* Median values.
† $P < 0.05$ *versus* bupivacaine plus fentanyl group.

panel). Analgesia was prolonged in the epinephrine groups regardless of whether the patients received 10 ml (160 ± 6 *vs.* 136 ± 7 min) or 15 ml (182 ± 7 *vs.* 130 ± 10 min) of solution ($P < 0.05$). Blood pressure decreased more in those receiving epinephrine (fig. 2) but the incidence of hypotension requiring ephedrine did not differ between groups (6% of patients in the plain group and 10% of patients in the epinephrine group). Heart rate increased slightly in the epinephrine group and decreased slightly in the plain group (fig. 2), although this difference was not significant.

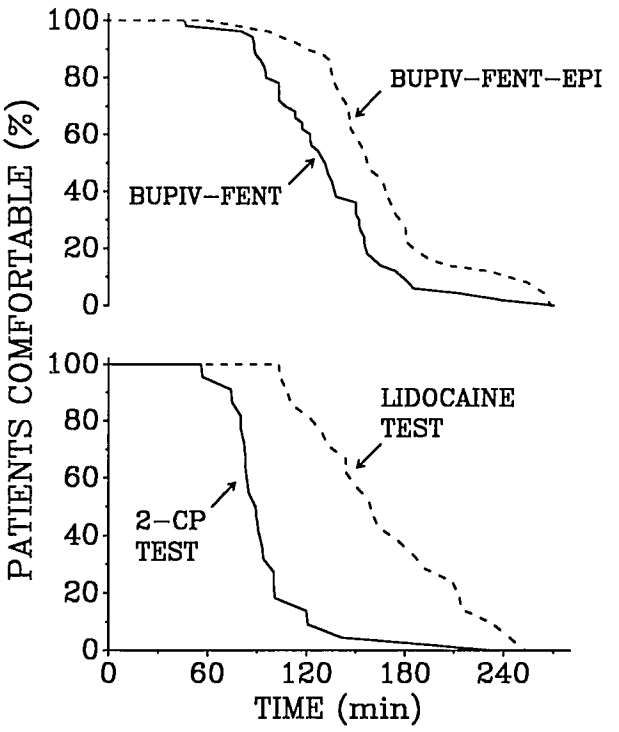

FIG. 1. Duration of analgesia after epidural injection of 0.25% bupivacaine with fentanyl, 5 μg/ml (solid line), or this combination with epinephrine, 3.33 μg/ml alone (dashed line, upper panel) or preceded by catheter testing with 2-chloroprocaine (solid line) or lidocaine (dashed line, lower panel). Each pair differ by logrank test.

PART 2: EFFECT OF 2-CHLOROPROCAINE

Fifty women (25 in the 2-chloroprocaine group, and 25 in the lidocaine group) provided data for analysis. The groups did not differ in demographic or labor data (table 3). The mean baseline pain score was 8.1 for the 2-chloroprocaine test-dose group and 8.2 for the lidocaine group. All cesarean sections were performed because of cephalopelvic disproportion, failure to progress, or fetal stress. Three neonates had a 1-min Apgar score of less than 7.

Although the groups did not differ in cephalad spread of sensory analgesia or onset of pain relief, duration of analgesia was significantly longer in the lidocaine group than in the 2-chloroprocaine group (table 4; fig. 1, lower panel). Blood pressure, heart rate, and incidence of hypotension did not differ between the groups.

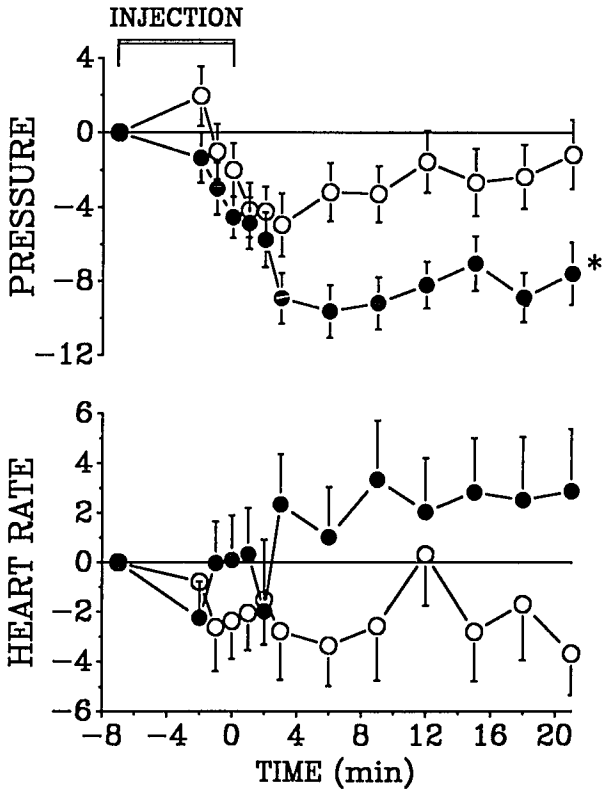

FIG. 2. Blood pressure and heart rate after epidural injection of 0.25% bupivacaine with fentanyl, 5 μg/ml (○), or this combination with epinephrine, 3.33 μg/ml (●). Two milliliters of local anesthetic solution were injected epidurally at time = −7, 5 ml at time = −2, and 3 ml at time = 0 min. Data are expressed as percent change from baseline. Each point represents the mean ± SEM of 43–50 patients. *Groups differ for blood pressure by analysis of covariance.

TABLE 3. Labor and Demographic Data: Study Part 2

Parameter	2-Chloroprocaine (n = 25)	Lidocaine (n = 25)
Age	24 ± 1.2	28 ± 0.6
Height (cm)	164 ± 1.3	162 ± 1.5
Weight (kg)	75 ± 2.8	71 ± 2.9
Nullipara	17 (68%)	14 (56%)
First stage (min)	518 ± 55	513 ± 52
Second stage (min)	81 ± 13	96 ± 12
Cesarean section	4 (16%)	3 (12%)

No significant differences.

Discussion

Combination drug therapy may decrease toxicity by decreasing the dose of each component, and may be logically applied to epidural analgesia during labor. Epidurally administered local anesthetics, opioids, and adrenergic agonists may produce bothersome or dangerous side effects in mother or fetus when administered in large doses.[8-11] The combination of local anesthetic, opioid, and adrenergic agonist examined in this study is composed of agents with demonstrated safety when injected epidurally and that activate separate mechanisms to produce analgesia.

Effect of Epinephrine

Epinephrine enhances analgesia produced by epidurally administered local anesthetics.[3,12] This effect may be due to local vasoconstriction, which would delay vascular uptake of local anesthetic. However, this mechanism may be less relevant for bupivacaine, which itself decreases local blood flow,[13] and whose vascular absorption following epidural injection is minimally altered by epinephrine.[12] Alternatively, epinephrine without local anesthetic may produce analgesia,[14] presumably by activating spinal α_2-adrenoceptors[15] and this analgesia may be additive with that produced by bupivacaine.

Epinephrine also enhances analgesia produced by epidurally administered opioids. Following cesarean section, epinephrine hastens onset, improves quality, and prolongs duration of epidurally administered diamorphine[16] and hydromorphone.[17] These results and those of this study likely reflect synergism between α-adrenergic agonists and opioids at spinal sites.[18,19]

The current study is a logical extension of a previous study of similar design performed at the same institution examining the effect of epinephrine on epidural analgesia produced by bupivacaine.[3] Taken together, these studies suggest small increases in duration when epinephrine or fentanyl are added to bupivacaine, but a greater increase when both are added (fig. 3). These studies use simple parameters (onset and duration of analgesia following a single dose) with direct clinical applicability. Although relative analgesic potency of these solutions cannot be easily compared using this type of design, other methods defining potencies of similar solutions support these data.[20]

Epidurally administered epinephrine produces primarily β-adrenergic effects: vasodilatation, increased heart rate, and increased cardiac output.[21] In contrast to plain 0.25% bupivacaine for epidural analgesia during labor, addition of epinephrine, 3.33 μg/ml, increases heart rate slightly but does not increase the incidence of treatable hypotension.[3] Similar small effects were observed in this study. These hemodynamic effects are less than those observed in volunteers,[21] perhaps due to different epinephrine dose or the diminished β-adrenoceptor responsiveness during pregnancy.[22]

Effect of Test Dosing

The long-lasting analgesia provided by epidural administration of the bupivacaine-fentanyl-epinephrine mixture described above may be a significant advantage

TABLE 4. Analgesia after Test Doses Plus Bupivacaine/Fentanyl/Epinephrine

Parameter	2-Chloroprocaine (n = 25)	Lidocaine (n = 25)
Most cephalad sensory dermatome (thoracic)		
Right	8 ± 0.4 (8)*	8 ± 0.4 (9)*
Left	7 ± 0.4 (8)*	8 ± 0.4 (8)*
Analgesia onset (min)	4.1 ± 2.4	3.6 ± 1.2
Analgesia duration (min)*	91	164†

* Median values.
† $P < 0.05$ *versus* 2-chloroprocaine group.

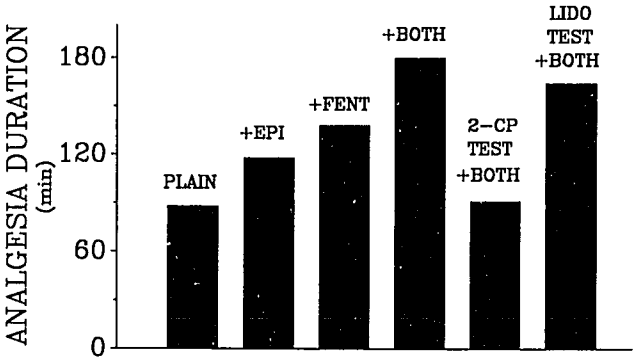

FIG. 3. Duration of analgesia after epidural injection of 10 ml of 0.25% bupivacaine plain,[3] or containing epinephrine 3.33 μg/ml,[3] fentanyl 5 μg/ml, or both. At right is duration of analgesia after epidural injection of the bupivacaine-fentanyl-epinephrine combination injected 2 min following epidural catheter test dosing with 2% 2-chloroprocaine or 2% lidocaine. Each bar represents the median duration, calculated from Kaplan-Meier analysis, of 25–50 patients.

on a busy labor service. However, this mixture may not safely and reliably identify iv catheter placement. Injection of 15 μg of epinephrine significantly decreases uterine blood flow in sheep,[23] and has been associated with transient fetal distress in humans.[4] For these reasons, many would prefer to test for possible iv catheter location before administering epinephrine containing solutions. Although the effect of iv local anesthetic injection on uterine blood flow is controversial,[8,9,24] either 100 mg of lidocaine or 2-chloroprocaine produce subjective symptoms when injected intravenously.[5,6] Consequently, in an effort to improve the safety of using a bupivacaine-fentanyl-epinephrine mixture for labor analgesia, plain 2-chloroprocaine or lidocaine can be used for catheter testing prior to the administration of the epinephrine containing solution.

This study shows that, compared with lidocaine, the use of 2-chloroprocaine as a test dose significantly shortens the subsequent duration of a bupivacaine-fentanyl-epinephrine mixture. 2-Chloroprocaine could alter the action of epidurally administered bupivacaine, fentanyl, or epinephrine. Corke *et al.*,[25] using an *in vitro* model of isolated rat sciatic nerves, found evidence that 2-chloroprocaine may interfere with the subsequent potency of bupivacaine, in agreement with the work of Hodgkinson *et al.*‡ in pregnant women. With regards to fentanyl, Malinow *et al.*[7] have shown that doses of 2-chloroprocaine adequate for cesarean section significantly shorten the duration of action of subsequently administered epidural fentanyl. This effect is not *p*H dependent,[26] but rather represents opiate antagonism.[27]§ Whether 2-chloroprocaine also inhibits analgesia due to spinal adrenoceptor activation has not been examined.

One could argue that the difference in analgesia duration observed in the two test-dose groups merely reflects the difference in duration of action of 2-chloroprocaine and lidocaine. However, as shown in figure 3, prior injection of 2-chloroprocaine resulted in a duration of action of BFE (91 min) not different from injection of plain bupivacaine alone (88 min). In contrast, prior injection of lidocaine (which by itself would produce effective analgesia for only 60–90 min) did not alter the much longer activity of BFE (164 *vs.* 180 min; fig. 3). Consequently, we believe that the short duration of analgesia in the 2-chloroprocaine test-dose group is due to a factor or factors other than the short duration of 2-chloroprocaine.

Combination drug therapy is becoming more popular in obstetrical anesthesia as anesthesiologists work to provide long-lasting pain relief while minimizing potential side effects such as motor blockade, neonatal depression, or decreased uterine blood flow. This study suggests that diluted solutions of bupivacaine, fentanyl, and epinephrine may be combined to provide long-lasting epidural analgesia during labor. However, prior injection of 2-chloroprocaine, but not lidocaine, significantly decreases the duration of analgesia achieved with this bupivacaine-fentanyl-epinephrine mixture. If a bupivacaine-fentanyl-epinephrine mixture is chosen for labor analgesia, we recommend using lidocaine rather than 2-chloroprocaine for the initial test dose.

§ Personal communication and data presented at the Annual Meeting of the American Society of Anesthesiologists.

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