Anesthesiology
67:403–407, 1987

Epidural Fentanyl/bupivacaine Mixtures for Obstetric Analgesia

SHEILA E. COHEN, M.B., CH.B.,* SHIRLEY TAN, M.D.,† GEORGE A. ALBRIGHT, M.D.,‡ JERRY HALPERN, PH.D.§

In 1982, Justins *et al.*[1] administered fentanyl, 80 μg, with a "test dose" of 3 ml of bupivacaine 0.5%, and found that analgesia with this combination was more rapid in onset, more prolonged, and more complete than that produced by the same dose of bupivacaine alone. Since then, several groups[2–6] have reported that fentanyl, 50–150 μg, combined with bupivacaine 0.125%, 0.25%, or 0.5%, provided better analgesia than the local anesthetic alone. Since none of these investigators studied more than one concentration of bupivacaine or fentanyl, the effect of varying the dosage of either component of the combination has remained unknown. The aim of this study, therefore, was to compare the clinical efficacy and side effects of three combinations of fentanyl and bupivacaine with those of bupivacaine alone. Specifically, we wanted to answer the following questions: 1) does the addition of fentanyl to epidural bupivacaine improve analgesia and the progress of labor? 2) does a larger dose of fentanyl result in greater benefit? 3) are there advantages to employing a subanalgesic concentration of bupivacaine rather than a concentration that by itself would produce adequate analgesia? and 4) are maternal and neonatal side effects more frequent when higher doses of these drugs are used?

MATERIALS AND METHODS

The study was approved by the Human Subjects Committee and informed consent was obtained from all participants. The study population consisted of 82 healthy, term parturients in active labor (cervical dilatation between 2 and 6 cm) who had requested epidural analgesia. To be enrolled in the study, all subjects had to be more than 18 yr old, be at least 152 cm tall, and weigh less than 114 kg. Patients were excluded if there was fetal distress prior to administration of the epidural, or if cesarean section was anticipated.

Lumbar epidural block was performed at the L2/3 or L3/4 interspace, with patients in the sitting position. A test dose of 3 ml of 1% lidocaine with 1:200,000 epinephrine and the study drug were administered through the needle. Patients were randomly assigned to one of four groups, and received bupivacaine either alone or in combination with fentanyl, as shown in table 1. Saline was added as necessary, so that the volume injected was 11 ml in all groups. The final bupivacaine concentrations were, therefore: groups 1, 2, and 3, 0.205%; and group 4, 0.068%.¶ All treatments were administered in a double-blind manner. Drugs were prepared by a nurse or a physician not involved in the study. After administration of the initial dose, an epidural catheter was introduced. All subsequent injections were of 0.25% bupivacaine (preceded by a test dose of 3 ml of 1% lidocaine with epinephrine), and were given as indicated by the patient's comfort and the progress of labor. No supplementation was administered until at least 25 min had elapsed from injection of the study drug.

Following administration of the study drug and all subsequent doses, analgesia was evaluated subjectively by the patient, who noted the onset of pain relief, and objectively by one of the investigators, who documented the loss of sensation to pinprick. Assessments were made every 2 min until maximum block was achieved, and every 10 min thereafter until pain returned or two-segment regression of the block occurred. The severity of pain was assessed before the block, after maximum block had been attained (usually at 45 min), and then 1 h later (provided a refill had not intervened). Pain was evaluated using a 10-cm visual analog scale (where 0 represented no pain and 10 cm represented "the worst pain ever experienced"), and by a verbal pain score (0–4, where 0 = no pain and 4 = very severe pain). Postpartum, mothers were asked to rate their overall analgesia for labor and delivery from

* Professor of Anesthesia (Clinical), Department of Anesthesia.
† Fellow in Obstetric Anesthesia, Department of Anesthesia.
‡ Associate Professor of Anesthesia (Clinical), Department of Anesthesia.
§ Statistician, Department of Family, Community and Preventive Medicine (Division of Biostatistics).

Received from the Departments of Anesthesia, and Family, Community and Preventive Medicine (Division of Biostatistics), Stanford University School of Medicine, Stanford, California. Accepted for publication March 30, 1987.

Address reprint requests to Dr. Cohen: Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305.

Key words: Analgesics, narcotic: fentanyl. Anesthesia, obstetric. Anesthetic techniques: epidural narcotic. Bupivacaine.

¶ We also had originally intended to study patients receiving bupivacaine, 0.068% without fentanyl. However, we omitted this group in response to the Human Subjects Committee's concern that all patients receive treatments that were reasonably certain to provide analgesia.

TABLE 1. Composition of Study Drug

	n	Bupivacaine, 0.25% (ml)	Fentanyl (μg)*	Saline (ml)
Group 1 (control)	21	9	0	2
Group 2	22	9	50	1
Group 3	20	9	100	0
Group 4	19	3	100	6

* 50 μg = 1 ml.

0–2, where 0 = worse than expected, 1 = about as expected, and 2 = better than expected.

Motor block was assessed at hourly intervals after the first dose, and after each refill using a modification of Bromage's scale;[7] a score of 0–3 was assigned, with 0 representing no block, and 3, complete inability to move the lower extremities. Fetal heart rate was continuously monitored electronically. The presence and severity of maternal complications, including hypotension (defined as a systolic pressure below 100 mmHg, or a decrease of more than 20%), nausea, vomiting, pruritus, frequency of urinary catheterization, drowsiness, and respiratory depression (respiratory rate less than 10/min), were determined and recorded.

At delivery, the quality of maternal expulsive efforts (poor, fair, moderate, or good) were graded by the obstetric nurse. Neonates were evaluated by means of the time to sustained respiration (TSR), APGAR scores at 1 and 5 min (assigned by the pediatrician or obstetric nurse), umbilical arterial and venous blood gas analyses obtained from a doubly clamped segment of umbilical cord, and neurobehavioral examinations (the Neurologic and Adaptive Capacity Score[8]) performed at 15 min, 2–4 h, and 24 h of life. To ensure consistency, the latter were all performed by the same investigator. Both the obstetric nurse and the investigator were unaware of the identity of the study drug.

Data were analyzed using one-way analysis of variance, Kruskal-Wallis test, and, where differences existed, by Tukey's test for multiple intergroup comparisons. A P value of <0.05 was considered statistically significant.

TABLE 2. Maternal Characteristics, Cervical Dilatation, and Severity of Pain before Study Drug Administration

	Group 1 (n = 21)	Group 2 (n = 22)	Group 3 (n = 20)	Group 4 (n = 19)
Age (yr)	27 ± 1	30 ± 1	27 ± 1	28 ± 1
Weight (kg)	74 ± 3	76 ± 3	74 ± 2	75 ± 3
Height (inches)	64 ± 1	64 ± 0	65 ± 1	64 ± 1
No. of primipara	9	9	13	12
Cervical dilatation (cm)	4.4 ± 0.3	3.5 ± 0.3	4.2 ± 0.4	4.4 ± 0.3
Visual analog score (0–10 cm)	7.2 ± 0.5	7.0 ± 0.5	7.6 ± 0.4	7.1 ± 0.4
Verbal pain score (0–4)	3.6 ± 0.1	3.4 ± 0.2	3.5 ± 0.2	3.3 ± 0.2

Values are mean ± SEM; no significant differences.

RESULTS

Group Characteristics and Analgesic Efficacy. The groups were similar with respect to maternal age, weight, height, parity, cervical dilatation, and the severity of pain prior to the block (table 2). With respect to the onset, duration, and quality of analgesia, groups 2 and 3 were similar (fig. 1). Thus, for these analyses, we combined group 2 (9 ml of bupivacaine 0.25% with 50 μg of fentanyl) and group 3 (9 ml of 0.25% bupivacaine with 100 μg of fentanyl). This group subsequently is referred to as group 2-3.

Generally, there were few statistically significant differences among the groups. However, analgesia in group 2-3 tended to begin sooner, to last longer, and to be more intense (lower visual analog and verbal pain scores 1 h following the block) than that in either groups 1 or 4. The only statistically significant differences were in the duration of analgesia ($P < 0.05$) and verbal pain score ($P < 0.01$) in group 2-3 compared with group 4. Verbal pain scores in group 2-3 also tended to be lower than those in group 1 ($P < 0.1$). Assessments of duration of analgesia obtained by pinprick yielded comparable results to those obtained subjectively (fig. 1), with two-segment regression of the block preceding the return of pain by about 4–5 min. The time to achieve maximal block (16–20 min), and the number of spinal segments blocked (8–9) were similar in all groups. There were no differences among the groups with respect to the onset and duration of analgesia obtained with subsequent refills, the hourly dosage of 0.25% bupivacaine administered throughout labor (4.5–6.3 ± 0.6 ml, mean ± SEM), or the number of refills. Mothers in all groups were equally satisfied with their analgesia, with 84–90% of patients rating their analgesia as "better than expected."

Effects on Labor and Delivery. Data for the duration of the first stage of labor showed a similar pattern to that seen for analgesia (fig. 2). Groups 2 and 3, therefore, were combined for this analysis, as well. The duration of the first, but not the second, stage of labor was shorter in group 2-3 than in group 1 ($P < 0.1$) or group 4 ($P < 0.05$) (fig. 2). Maternal expulsive efforts at delivery were rated as excellent in 89–95% of patients in all

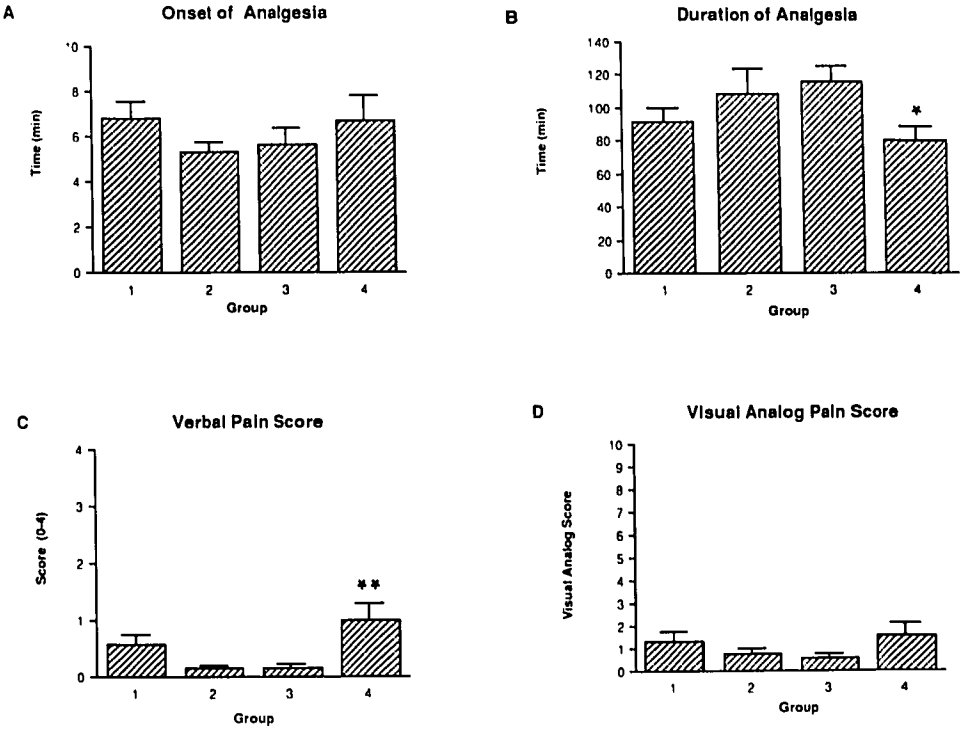

FIG. 1. Analgesic properties of study treatments (mean ± SEM). *A.* Onset of analgesia (subjective). *B.* Duration of analgesia (subjective). *C.* Verbal pain score. *D.* Visual analog pain score. *$P < 0.05$ group 4 *versus* group 2–3. **$P < 0.01$ group 4 *versus* group 2–3.

groups. Mode of delivery did not differ among the groups: 32–47% required forceps deliveries, while cesarean section was performed in 5–16% of women. Uterine hypertonus did not occur in any patient, and the same number of patients in each group required augmentation of labor with oxytocin following the block.

Side Effects. Motor block was minimal or absent following administration of the study drug in all groups. It became more dense after the first refill, when it was significantly greater in group 3 than in the other groups ($P < 0.05$; fig. 3). The incidences of other side effects are shown in table 3. With the exception of mild, transient pruritus, which occurred in approximately 30% of all patients who received fentanyl, and drowsiness, which occurred in 11% of women in group 4, side effects were most common in the control group.

Fetal/Neonatal Effects. Decreased fetal heart rate variability following injection of the study drug occurred in two babies in each of groups 1 and 4. Fetal bradycardia occurred with similar frequency in the groups (4–6 cases in each group). Neonatal condition, as measured by TSR, Apgar scores, and neurobehavioral scores, was good and, apart from TSR (which was longer in group 1) was similar in all groups (table 4). Umbilical cord blood gases also did not differ among the groups (table

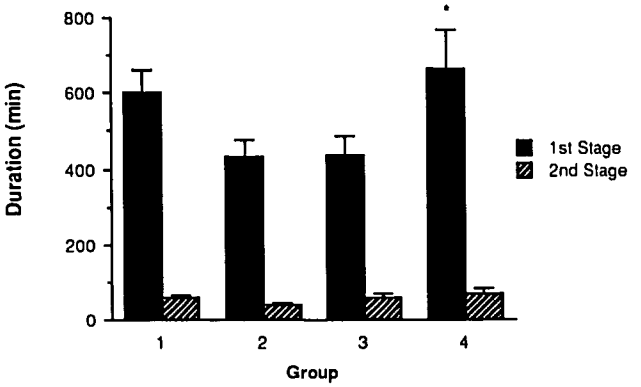

FIG. 2. Duration of first and second stages of labor (mean ± SEM). *$P < 0.05$ group 4 *versus* group 2-3.

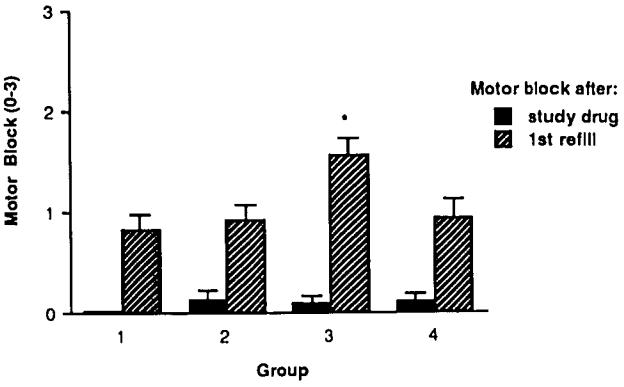

FIG. 3. Motor block (scored 0–3) 1 h following administration of study drug and first refill (mean ± SEM). *$P < 0.05$.

TABLE 3. Percentage of Patients in Each Group Experiencing Side Effects

	Group 1	Group 2	Group 3	Group 4
Hypotension	14	0	5	11
Nausea	14	5	5	0
Vomiting	9*	0	0	0
Pruritus	0*	32	30	26
Drowsiness	5	0	0	11
Urinary retention	33	9	10	21

* $P < 0.05$.

5). One baby in the control group required mask ventilation at birth, and no infant required naloxone administration or endotracheal intubation other than electively, as part of the protocol used for removal of meconium.

DISCUSSION

Initially, epidurally administered opioids provided promise as ideal analgesics for labor, because of their selective effect on perception of pain and sparing of motor, autonomic, and other sensory modalities. Unfortunately, morphine is relatively ineffective in this respect,[9-11] and, while fentanyl[12] and meperidine[13] provide better analgesia, it is of short duration and is inadequate for the second stage of labor. Since several investigators had reported an additive or synergistic effect of epidural opioids with local anesthetics[14] (particularly fentanyl and bupivacaine[1-6]), one of our goals was to determine whether the efficacy of such combinations merited their adoption for routine use during labor.

TABLE 4. Newborn Characteristics

	Group 1	Group 2	Group 3	Group 4
Weight* (kg)	3.61 ± 0.1	3.65 ± 0.1	3.57 ± 0.1	3.49 ± 0.1
Time to sustained respiration* (s)	41 ± 5‡	29 ± 3	27 ± 3	32 ± 4
Apgar score† <7 at:				
1 min	3	0	2	2
5 min	0	0	0	1
N.A.C.S.† <35 at:				
15 min	3	1	2	2
2–4 h	1	1	1	2
24 h	0	0	0	0

A score greater than 35 in the Neurologic and Adaptive Capacity Score indicates a healthy and alert baby.
* Values are mean ± SEM.
† Values represent numbers of patients.
‡ $P < 0.05$.

TABLE 5. Umbilical Cord Blood Gas Analyses

	Group 1	Group 2	Group 3	Group 4
Umbilical vein:				
*p*H	7.36 ± 0.01	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01
P_{CO_2}	40 ± 1	41 ± 1	42 ± 1	39 ± 2
P_{O_2}	28 ± 1	29 ± 1	28 ± 1	31 ± 2
HCO_3	20.9 ± 1.1	22.8 ± 0.5	23.0 ± 0.4	22.5 ± 0.9
Umbilical artery:				
*p*H	7.0 ± 0.28	7.28 ± 0.01	7.28 ± 0.01	7.25 ± 0.02
P_{CO_2}	49 ± 2	50 ± 1	50 ± 3	49 ± 4
P_{O_2}	18 ± 1	19 ± 1	20 ± 2	23 ± 2
HCO_3	22.2 ± 0.8	23.7 ± 0.6	22.9 ± 0.8	22.3 ± 1.2

Values are mean ± SEM; no significant differences.

Our results demonstrated a tendency towards improved analgesia and shorter duration of labor, but no statistically significant differences, when fentanyl was added to 9 ml of 0.25% bupivacaine, as compared with the same dose of bupivacaine alone. Statistical significance was achieved for only a few variables, and then only between the combined group 2-3 and group 4. This is probably due to the fact that the analgesia obtained with a lidocaine test dose and 9 ml of 0.25% bupivacaine by itself is already quite good. In retrospect, it might have been better if we had avoided the test dose before the study drug and each reinjection; the lidocaine may have intensified analgesia in the control group and made it more difficult to demonstrate the potentiating effect of fentanyl on bupivacaine. While administration of a test dose in labor epidurals is now somewhat controversial, at the time the study was started, it was considered standard practice.

In contrast to our findings, most of the previous studies have reported significant potentiation of epidural bupivacaine by fentanyl. However, in all these studies, the control group received relatively small doses of bupivacaine (3 ml of 0.5%;[1,5,6] 6 ml of 0.25%;[2] 10 ml of 0.125%[3]), and significant improvement in analgesic effect was possible. Since such small doses are not usually employed for the initial injection because they frequently fail to produce adequate analgesia, we compared the combination of bupivacaine-fentanyl with a more commonly used analgesic dose, as well as with a subanalgesic dose of bupivacaine. Although we were not able to study 0.068% bupivacaine alone, the fact that analgesia in group 4 (0.068% bupivacaine with fentanyl, 100 μg) was similar to that in the control group suggests that the narcotic did indeed potentiate this very dilute solution of local anesthetic.

Our results do not support routinely adding fentanyl

to 0.25% bupivacaine. However, marginal benefits may result from this technique that justify its use in certain circumstances, *e.g.*, in prolonged labors, or if pain is unrelieved by moderate doses of local anesthetic. While our conservative view is shared by Vella *et al.*,[6] the use of epidural fentanyl has become quite widespread on the basis of early reports of its success. It has been claimed that its major advantage is that it permits administration of subanesthetic concentrations of local anesthetic. However, with respect to analgesia, side effects, the duration of labor, and neonatal effects, we demonstrated no advantages for the patients in group 4 who received fentanyl in combination with a very low concentration of bupivacaine.

It is of interest that the duration of labor was shorter in groups 2 and 3, and that analgesia in these groups was also somewhat superior. Although we can only speculate as to whether these factors are associated, it is possible that better relief of pain and anxiety results in greater inhibition of maternal catecholamines, particularly epinephrine, which is known to inhibit uterine contractility.[15] We found no evidence to support the anecdotal reports of uterine hypertonus, which has been said to occur following the administration of epidural fentanyl.[2]

In summary, we found that the addition of epidural fentanyl, 50 or 100 μg, to 9 ml of 0.25% bupivacaine did not result in a statistically significant improvement in analgesia when compared with the local anesthetic alone. Analgesia with these combinations was, however, significantly better than that obtained by adding fentanyl, 100 μg, to 3 ml of 0.25% bupivacaine (group 4, final bupivacaine concentration 0.068%). We believe that the finding of comparable analgesia in group 4 and the control group does suggest that the narcotic potentiated this subanalgesic concentration of bupivacaine. No advantage appeared to result from use of the larger dose of fentanyl, which was associated with more profound motor block after the first refill. The addition of fentanyl to epidural bupivacaine was not associated with an increase in maternal or fetal/neonatal side effects, other than mild transient pruritus which did not require treatment.

References

1. Justins DM, Francis D, Houlton PG, Reynolds F: A controlled trial of extradural fentanyl in labor. Br J Anaesth 54:409–414, 1982
2. Desprats R, Mandry J, Grandjean H, Amar B, Pontonnier G, Lareng L: Analgesie peridurale au cours du travail: Etude comparative de l'association fentanyl-marcaïne et de la marcaïne seule. J Gynecol Obstet Biol Reprod (Paris) 12:901–905, 1983
3. Youngstrom R, Eastwood D, Patel H, Bhatia R, Cowan R, Sutheimer C: Epidural fentanyl and bupivacaine in labor: Double-blind study. ANESTHESIOLOGY 61:A414, 1984
4. Skerman JH, Thompson BA, Goldstein MT, Jacobs MA, Gupta A, Blass NH: Combined continuous epidural fentanyl and bupivacaine in labor: A randomized study. ANESTHESIOLOGY 63:A450, 1985
5. Justins DM, Knott C, Luthman J, Reynolds F: Epidural versus intramuscular fentanyl. Anaesthesia 38:937–942, 1983
6. Vella LM, Willats DG, Knott C, Lintin DJ, Justins DM, Reynolds F: Epidural fentanyl in labor. Anaesthesia 40:741–747, 1985
7. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand (Suppl 1) 16:55–69, 1965
8. Amiel Tison C, Barrier G, Shnider SM, Levinson G, Hughes SC, Stefani SS: A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term neonates. ANESTHESIOLOGY 56:340–350, 1982
9. Booker PD, Wilkes RG, Bryson THL, Bedders J: Obstetric pain relief using epidural morphine. Anaesthesia 35:377–379, 1980
10. Husemeyer RP, O'Connor ML, Davenport HT: Failure of epidural morphine to relieve pain in labour. Anaesthesia 35:161–163, 1980
11. Hughes SC, Rosen MA, Shnider SM, Abboud TK, Stefani SJ, Norton M: Maternal and neonatal effects of epidural morphine for labor and delivery. Anesth Analg 63:319–324, 1984
12. Carrie LES, O'Sullivan GM, Seegobin R: Epidural fentanyl in labour. Anaesthesia 36:965–969, 1981
13. Perris BW: Epidural pethidine in labour—A study of dose requirements. Anaesthesia 35:380–382, 1980
14. Baraka A, Maktabi M, Noueiheid R: Epidural meperidine-bupivacaine for obstetric analgesia. Anesth Analg 61:652–656, 1982
15. Lederman RD, Lederman E, Work B, McCann DS: Anxiety and epinephrine in multiparous women in labor: Relationship to duration of labor and fetal heart rate pattern. Am J Obstet Gynecol 153:870–877, 1985
16. Neumark J, Hammerle AF, Biegelmayer CH: Effects of epidural analgesia on plasma catecholamine and cortisol in parturition. Acta Anaesthesiol Scand 29:555–559, 1985