# Placental Transfer and Neonatal Effects of Epidural Sufentanil and Fentanyl Administered with Bupivacaine during Labor 

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Background：This randomized double－blind investigation was designed to study the placental transfer and neonatal ef－ fects of epidural sufentanil and fentanyl infused with bupi－ vacaine for labor analgesia．
Methods：Healthy parturient women $(\mathrm{n}=36)$ received epi－ dural bupivacaine alone（group B）or with fentanyl（group B－ F）or sufentanil（group B－S）．Group B received a $12-\mathrm{ml}$ bolus of $0.25 \%$ bupivacaine followed by a $10 \mathrm{ml} / \mathrm{h}$ infusion of $0.125 \%$ bupivacaine．Groups B－F and B－S received a $12-\mathrm{ml}$ bolus of $0.125 \%$ bupivacaine with $75 \mu \mathrm{~g}$ fentanyl or $15 \mu \mathrm{~g}$ sufentanil， respectively，followed by $10 \mathrm{ml} / \mathrm{h}$ of $0.125 \%$ bupivacaine with fentanyl $1.5 \mu \mathrm{~g} / \mathrm{ml}$ or sufentanil $0.25 \mu \mathrm{~g} / \mathrm{ml}$ ．Maternal venous （MV）and umbilical arterial（UA）and umbilical venous（UV） bupivacaine and opioid plasma concentrations were deter－ mined．Neonatal assessment included Apgar scores，umbilical cord blood gas analyses，and neurobehavioral testing at de－ livery and at 2 and 24 h of life using the Neurologic and Adap－ tive Capacity Score（NACS）．
Results：The mean total dose of fentanyl was $136.6 \pm 13.1 \mu \mathrm{~g}$ （SEM），and of sufentanil， $23.8 \pm 1.8 \mu \mathrm{~g}$ ．Although administered in a ratio of 5．7：1，fentanyl and sufentanil MV plasma concen－ trations were in the ratio of 27：1．UV／MV ratios were 0.37 for fentanyl and 0.81 for sufentanil．Fentanyl was detected in most UA samples，whereas sufentanil was present in only one sam－ ple．Neonatal condition was good and generally similar in all groups，with the exception of a lower NACS at 24 h in group B－F．
Conclusions：Although the degree of placental transfer of sufentanil appeared greater than that of fentanyl，lower MV

[^0]sufentanil concentrations resulted in less fetal exposure to sufentanil．The lower NACS at 24 h in group B－F may reflect the continued presence of fentanyl in the neonate．（Key words： Analgesics，opioid：fentanyl；sufentanil．Anesthesia：obstetric． Anesthetic techniques：epidural．）

EPIDURAL sufentanil and fentanyl are administered routinely in combination with bupivacaine to enhance analgesia during labor and delivery．The effects of epi－ dural local anesthetic－opioid combinations on the parturient woman and the course of labor have been well documented．${ }^{1-4}$ However，there is little infor mation regarding the accumulation of epidurally ad ministered lipophilic opioids in the newborn and of possible adverse neonatal effects．This prospective double－blind study was primarily designed to deter－ mine fetal and maternal plasma opioid concentrations after epidural sufentanil－bupivacaine and fentanyl－ bupivacaine mixtures administered for labor and de livery and to assess neonatal neurobehavioral status Information regarding analgesic efficacy and side effects also was obtained．

## Materials and Methods

After approval of the study by the Human Subjects Committee，written informed consent was obtained from 36 healthy，term parturient women with uncom－ plicated pregnancies who requested epidural analgesia during labor．No subject had received any analgesic drugs before enrolling in the study．Patients were ran－ domly assigned to receive plain bupivacaine（group B； $\mathrm{n}=13$ ），bupivacaine with fentanyl（group B－F； $\mathrm{n}=$ 14），or bupivacaine with sufentanil（group B－S；$n=9$ ） in a double－blind manner．Group assignments were de－ termined by a random numbers table and were sealed in sequentially numbered envelopes．Study solutions were freshly prepared by an anesthesiologist not in－ volved in patient management or data collection．Epi－
group $B-F$ ，and 12 ml 0 S． 25 $\mathrm{g} / \mathrm{ml}$ sufentanil $(15 \mu \mathrm{~g})$ 弟 gro ater，a continuous epidu豙al in $\mathrm{m} / \mathrm{h}$ with group $B$ recẽ． group $B-F$ receiving $0.12 \%$ bu $1.5 \mathrm{\mu g} / \mathrm{ml}$ and group $\mathrm{B}-\mathrm{S}$ remeiv plus sufentanil $0.25 \mu \mathrm{~g} \underset{-}{\text { g．}} \mathrm{ml}$ ． treated with $5-\mathrm{ml}$ boluse ${ }_{3}^{3}$ ，of by increasing the epidurais infu infusion rate was decreased $b$ the sensory level was too $\frac{\text { andigh }}{6}$ sidered excessive．The ep $\overline{\frac{\bar{Q}}{2}} \mathrm{~d}$ ura throughout the second s总ge u Data were obtained by hin inv treatment．Analgesia waswasses $100-\mathrm{mm}$ visual analog p ©in sc no pain and $100=$ worsị̆ pos maternal blood pressure，零eart were recorded at $5-\mathrm{min}$ ginterv $a t 60 \mathrm{~min}$ ，and then hourl unti observations were record ${ }^{\circ} \mathrm{d}$ at of sensory blockade to poginpri block according to a médifie range of motion of hips，lagnees， of knees and feet only $\stackrel{2}{2} 1, \mathrm{~m}$ 2，and inability to move his ${ }_{\substack{0}}^{\text {pen }} \mathrm{ps}$ （rated $0-3$ ，where $0=$ n＠ne， and $3=$ vomiting）；prurtritus（ none， $1=$ mild， $2=$ medera requiring treatment），aixd sc where $0=$ none， $1=$ mild， extreme）．The patient rated effect．Urinary retention was patient＇s bladder required catl the time of delivery was ra rioman on a scale of $0-3$ ，wh Neona and $3=$ excellent． tespiration，1－and 5－min Apga and Adaptive Capacity Scores

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dural catheters were inserted via the L2-L3 or L3-L4 interspace by a standard technique. All patients received a $10-15 \mathrm{ml} / \mathrm{kg}$ intravenous infusion of lactated Ringer's solution before epidural block. An epinephrine test dose was not used. An initial $12-\mathrm{ml}$ dose of study solution was administered incrementally through the epidural catheter over a 2 -min period. This consisted of $12 \mathrm{ml} 0.25 \%$ bupivacaine in group B, 12 ml $0.125 \%$ bupivacaine plus $6.25 \mu \mathrm{~g} / \mathrm{ml}$ fentanyl ( $75 \mu \mathrm{~g}$ ) in group $B-F$, and $12 \mathrm{ml} 0.125 \%$ bupivacaine plus 1.25 $\mu \mathrm{g} / \mathrm{ml}$ sufentanil ( $15 \mu \mathrm{~g}$ ) in group B-S. Twenty minutes later, a continuous epidural infusion was started at 10 $\mathrm{ml} / \mathrm{h}$ with group B receiving $0.125 \%$ bupivacaine, group B-F receiving $0.125 \%$ bupivacaine plus fentanyl $1.5 \mu \mathrm{~g} / \mathrm{ml}$ and group B-S receiving $0.125 \%$ bupivacaine plus sufentanil $0.25 \mu \mathrm{~g} / \mathrm{ml}$. Breakthrough pain was treated with $5-\mathrm{ml}$ boluses of $0.25 \%$ bupivacaine and by increasing the epidural infusion rate by $2 \mathrm{ml} / \mathrm{h}$. The infusion rate was decreased by $2 \mathrm{ml} / \mathrm{h}$ increments if the sensory level was too high or motor block was considered excessive. The epidural infusion was continued throughout the second stage until delivery.
Data were obtained by an investigator blinded to the treatment. Analgesia was assessed by the patient on a $100-\mathrm{mm}$ visual analog pain scale (VAPS), where $0=$ no pain and $100=$ worst possible pain. Pain scores, maternal blood pressure, heart rate and respiratory rate were recorded at $5-\mathrm{min}$ intervals for the first 30 min , at 60 min , and then hourly until delivery. The following observations were recorded at the same times: the level of sensory blockade to pinprick; the degree of motor block according to a modified Bromage scale ${ }^{5}$ (full range of motion of hips, knees, and feet $=0$, movement of knees and feet only $=1$, movement of feet only $=$ 2 , and inability to move hips, knees, or feet $=3$ ); nausea (rated $0-3$, where $0=$ none, $1=$ mild, $2=$ moderate, and $3=$ vomiting) ; pruritus (rated as $0-3$, where $0=$ none, $1=$ mild, $2=$ moderate, and $3=$ severe and requiring treatment), and somnolence (rated $0-3$, where $0=$ none, $1=$ mild, $2=$ moderate, and $3=$ extreme). The patient rated the severity of each side effect. Urinary retention was considered present if the patient's bladder required catheterization. Analgesia at the time of delivery was ranked by the parturient woman on a scale of $0-3$, where $0=$ poor, $1=$ fair, 2 $=$ good, and $3=$ excellent.
Neonatal evaluation included the time to sustained respiration, 1 - and $5-\mathrm{min}$ Apgar scores, and Neurologic and Adaptive Capacity Scores (NACS) ${ }^{6}$ at $15 \mathrm{~min}, 2 \mathrm{~h}$, and 24 h after birth. The NACS is designed to screen
neonates for central nervous system depression and to differentiate central nervous system depression from asphyxia, trauma, or drug effect. The test has 20 criteria, divided into five categories: (1) adaptive capacity, (2) passive tone, (3) active tone, (4) primary reflexes, and (5) alertness. Neonates are given a rank of $0-2$ for each neùrobehavioral item where $0=$ absent or grossly abnormal, $1=$ mediocre or slightly normal, and $2=$ vigorous or normal.
At the time of delivery, umbilical arterial (UA) and umbilical venous (UV) blood was obtained from a doubly clamped segment of umbilical cord for blood gas analyses ( $p \mathrm{H}$-blood gas analyzer model 178, Corning, Medfield, MA, with calculation of $\mathrm{HCO}_{3}{ }^{-}$values) and for determination of bupivacaine and opioid drug concentrations. Maternal blood was also obtained from an antecubital vein for the latter purpose. Blood was centrifuged and the plasma frozen for stibse, rent assay.
Plasma fentanyl and sufentanil concentrations were determined by gas chromatography-mass spectrometry using the modification described below of the method of Woestenborghs et al. ${ }^{7}$ to increase sensitivity. This method consists of a multistep liquid-liquid extraction of plasma, concentration of the extract, and gas chro-matography-mass spectrometry analysis of the extracts. An internal standard was used to correct for drug recovery throughout the extraction and analytical process. Selected ion monitoring was used to increase sensitivity. Our analytical limit of detection was $0.01 \mathrm{ng} /$ ml for both fentanyl and sufentanil. We made several modifications to our standard sufentanil assay to achieve these levels. Samples were analyzed only after a rigorous cleaning of the mass spectrometer source and injector. We also injected one fifth of our sample extract using an increased injector pressure technique to transfer sample more fully onto the column. The interday coefficient of variation was $11.5 \%$ at $0.02 \mathrm{ng} /$ ml . Plasma bupivacaine concentrations were measured with a gas chromatograph system (Hewlett-Packard) with a nitrogen phosphorus detector using an internal standard. The lower level of detection was $0.1 \mathrm{ng} / \mathrm{ml}$ and the interday coefficient of variation was $5.7 \%$ at 10 $\mathrm{ng} / \mathrm{ml}$ bupivacaine.
Maternal and neonatal demographic data were analyzed by analysis of variance (ANOVA), chi-squared analysis, and Fisher's exact test as appropriate. Evaluation of nausea, pruritus and somnolence included calculating an hourly average side effect score for each symptom by dividing the sum of the hourly side effect rankings by the total hours the patient received epidural
analgesia．The frequencies of side effects were com－ pared by chi－squared analysis and hourly side effect scores were compared by the Kruskal－Wallis test．VAPS， as well as maternal hemodynamic and respiratory data， were analyzed by ANOVA and repeated measures AN－ OVA．Kruskal－Wallis test was used to compare Apgar scores and NACS．If significant overall differences among the groups were detected，intergroup compar－ isons were further investigated with Fisher＇s progressive least squares difference test or Dunnett＇s $t$ test（after ANOVA），and the Mann－Whitney test with the Bonfer－ roni correction for multiple comparisons（after the Kruskal－Wallis test）．When chi－squared analysis indi－ cated an overall difference among the groups，each pair of groups was then compared separately and the Bon－ ferroni correction applied．Correlation between vari－ ables of continuous data was determined with Fisher＇s $r$－to－$z$ correlation coefficient．Data are expressed as the mean $\pm$ SEM except where otherwise noted．$P<0.05$ was considered significant．

## Results

The groups were similar with respect to maternal age， height，and weight（table 1）．Group B－S had signifi－ cantly more nulliparous women than did the other two groups．Patients in the three groups had similar pre－ epidural VAPS，and all groups obtained satisfactory an－ algesia as demonstrated by a reduction in VAPS in the first 10 min after initiating epidural analgesia（fig．1）． Analgesia was better in group B－S at 20 min after ini－ tiation of epidural analgesia（ $P<0.05 v s$ ．group B－F； fig．1）and at $2 \mathrm{~h}(P<0.05 v s$ ．group B－F）；however， there were no differences at any other time until de－ livery．Analgesia in the three groups also was compa－ rable in terms of the number of supplemental injections required for breakthrough pain，the total dose of bu－

Table 1．Maternal Characteristics

|  | Bupivacaine <br> $(\mathrm{n}=13)$ | Bupivacaine－ <br> Sufentanil <br> $(\mathrm{n}=9)$ | Bupivacaine－ <br> Fentanyl <br> $(\mathrm{n}=14)$ |
| :--- | :---: | :---: | ---: |
| Age（yr） | $27 \pm 2$ | $28 \pm 2$ | $29 \pm 2$ |
| Height（cm） | $166 \pm 2$ | $162 \pm 2$ | $162 \pm 2$ |
| Weight $(\mathrm{kg})$ | $77 \pm 3$ | $72 \pm 3$ | $75 \pm 4$ |
| Parity（no．of patients） <br> Nulliparous | 6 | $8^{*}$ | 5 |
| Parous | 7 | 1 | 9 |

[^1]

Fig．1．Maternal assessment of epidural analgesia．All groups experienced a reduction in visual analog pain scale（VAPS） score，with better analgesia at 20 min and 2 h in the group receiving bupivacaine（BUP）with sufentanil．＊$P<0.05$ ，BUP with sufentanil vs．BUP with fentanyl）．
pivacaine administered，the duration of infusion（table 2），and maternal assessment of analgesia at the time of delivery．All but one patient，who was in group B－F， rated analgesia for delivery as good or excellent．The mean total dose of sufentanil given was $23.8 \pm 1.8 \mu \mathrm{~g}$ （range $12.0-29.3 \mu \mathrm{~g}$ ）；the mean fentanyl dose was $136.6 \pm 13.1 \mu \mathrm{~g}$（range $80.0-265.0 \mu \mathrm{~g}$ ）．The groups were similar with respect to the duration of labor and the mode of delivery（table 2 ）．No patient underwent cesarean delivery．
The level of sensory blockade was similar for the three groups；upper levels ranged from T4－T10（median T8）． There were no significant changes in maternal mean arterial pressure，heart rate or respiratory rate after epi－ dural analgesia in any of the groups，and no significant differences among the groups．The incidence of nausea was $38 \%, 15 \%$ ，and $0 \%$ for groups B，B－F and B－S re－ spectively，with no statistically significant differences in frequency（ $P=0.12$ ）or severity $(P=0.13)$ ．No patient experienced vomiting or required treatment． Pruritus occurred in $0 \%$ of group B， $50 \%$ of group B－F and $38 \%$ of group $B-S$ patients $(P=0.04$ ，group $B v$ ． group B－F）．The average hourly pruritus score was greatest in the $B-F$ group（ $P=0.012$ vs．group $B$ ）， although no patient required treatment for pruritus． The incidence and intensity of motor blockade were similar in all groups，with $47 \%, 35 \%$ and $33 \%$ of groups B，B－F，and B－S respectively，having a 1 or 2 modified Bromage score．Only one patient，who was in group B developed a motor block score of 3 ．

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 than in groups $B$ and $B-S$ ． were compared，there w帯e no
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Table 3．Newborn Characteristics

$P=0.02(B-F$ vs．$B$ and $B-S)$ apacity
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Table 2. Labor Characteristics and Assessment of Analgesia

|  | Bupivacaine <br> $(\mathrm{n}=13)$ | Bupivacaine-Sufentanil <br> $(\mathrm{n}=9)$ | Bupivacaine-Fentanyl <br> $(\mathrm{n}=14)$ |
| :--- | :---: | :---: | :---: |
| Cervical dilation $(\mathrm{cm})$ at epidural placement | $3.9 \pm 0.4$ | $3.9 \pm 0.3$ | $3.9 \pm 0.3$ |
| Duration of stage 1 $(\mathrm{min})$ | $315 \pm 69$ | $311 \pm 79$ |  |
| Duration of stage 2 $(\mathrm{min})$ | $90 \pm 15$ | $89 \pm 25$ | $311 \pm 55$ |
| Mode of delivery (no. of patients) |  |  | $87 \pm 22$ |
| Spontaneous | 8 | 7 | 12 |
| Vacuum/forceps | 5 | 2 | 2 |
| Duration of epidural infusion (min) | $244 \pm 37$ | $315 \pm 38$ | $207 \pm 32$ |
| No. of supplemental injections | $1.5 \pm 0.4$ | $1.4 \pm 0.4$ | $1.6 \pm 0.3$ |
| Total bupivacaine dose $(\mathrm{mg})$ | $91.0 \pm 9.4$ | $91.0 \pm 12.9$ | $90.2 \pm 11.9$ |

Newborn characteristics and assessments are shown in table 3. Apgar scores at 1 and 5 min and times to sustained respiration were satisfactory and similar in the three groups. Total NACS were similar among the groups at 15 min and 2 h after delivery. However, at 24 h , NACS in the B-F group were significantly lower than in groups B and B-S. When NACS component scores were compared, there were no statistically significant differences among the groups. The pattern of decreased NACS in the B-F group did not suggest perinatal asphyxia or birth trauma, which is often characterized by imbalances of extensor and flexor tone of the neck muscles or hypotonia of the lower extremities. ${ }^{6}$ Umbilical cord blood gases were similar among the groups except for UV $\mathrm{CO}_{2}$ tension ( $\mathrm{P}_{\mathrm{CO}_{2}}$ ), which, although within normal limits, was significantly greater in group B-S infants (table 4).

Bupivacaine, sufentanil and fentanyl plasma concentrations are shown in tables 5 and 6 . Technical difficulties precluded obtaining sufficient UA blood for bupivacaine and opioid assays as well as for blood gas analyses in all cases. The mean UV bupivacaine concentration was significantly greater in group B-S than in the other two groups (table 5). Sufentanil was detected in all but one maternal venous (MV) and all UV samples, but was undetectable in 4 of 5 of the UA samples obtained (table 6). Fentanyl was detected in all MV, 12 of 13 UV , and 7 of 9 UA samples. The mean UV/MV ratios for each drug were obtained by calculating the ratio for each neonate and then averaging these values. There was a strong, statistically significant correlation between UV and MV drug concentrations for sufentanil (fig. 2) but not for fentanyl.

Table 3. Newborn Characteristics and Neonatal Assessment

|  | Bupivacaine <br> $(n=13)$ | Bupivacaine-Sufentanil <br> $(n=9)$ | Bupivacaine-Fentanyl <br> $(\mathrm{n}=14)$ |
| :--- | :---: | :---: | :---: |
| Gestatational age $(w k)$ | $39 \pm 0.3$ | $39 \pm 0.4$ | $40 \pm 0.3$ |
| Length (cm) | $52 \pm 1.2$ | $52 \pm 1.0$ | $51 \pm 0.9$ |
| Weight (gm) | $3,689 \pm 148$ | $3,569 \pm 159$ | $3,461 \pm 197$ |
| Gender (no. of infants) |  |  |  |
| Male | 6 | 6 | 6 |
| Female | 7 | 3 | 8 |
| Apgar $<7$ at 1 min | 2 | 1 | 0 |
| Apgar < 7 at 5 min | 0 | 0 | 0 |
| Time to sustained respiration (s) | $28 \pm 5$ | $28 \pm 11$ | $34 \pm 10$ |
| NACS at 15 min | $34.0 \pm 1.1$ | $32.7 \pm 0.9$ | $33.4 \pm 0.7$ |
| NACS at 2 h | $34.4 \pm 0.8$ | $34.0 \pm 0.6$ | $34.9 \pm 0.5$ |
| NACS at 24 h | $36.8 \pm 0.5$ | $37.1 \pm 0.4$ | $34.7 \pm 0.8^{*}$ |

[^2][^3]

UA = umbilical artery; UV = umbilical vein

* $P=0.003$


## Discussion

Several investigators have reported the effects of adding fentanyl or sufentanil to bupivacaine for labor analgesia. ${ }^{1-4}$ In general, the addition of these lipophilic opioids to bupivacaine has improved labor analgesia and maternal satisfaction while allowing the administration of smaller quantifies of local anesthetic. ${ }^{1,8,9}$ The resultant reduction in motor blockade has been accompanied in some studies by a decreased number of instrumental deliveries. ${ }^{8,9}$ Although the benefits of this technique have been well documented for the parturient woman, the effect of epidural opioids on the neonate are not as well understood. Although clinically significant neonatal depression appears rare after maternal epidural opioid administration, ${ }^{2-4}$ the potential for this complication certainly exists. In one study, ${ }^{10} 50-80-\mu \mathrm{g}$ doses of epidural sufentanil given during cesarean delivery caused minor neonatal depression, and epidural fentanyl may have caused respiratory depression in two infants in another cesarean study. ${ }^{11}$ Carric et al. ${ }^{12}$ also described respiratory depression in one infant when relatively large doses of epidural fentanyl were used without local anesthetics to provide labor analgesia. In all of these studies large doses of opioids were administered or an opioid bolus was given shortly before delivery. The current investigation was designed to evaluate the effects of fentanyl and sufentanil as they are used in current obstetric anesthesia practice: as a modest bolus dose followed by a low-dose infusion in combination with dilute bupivacaine.
$\mathbb{\$}$ Kick O, Vertommen JD, Van Aken H, Gryseels J: Sufentanil: Ma ternal and neonatal plasma levels after epidural administration during labor and delivery (abstract). Anesthesiology 75:A837, 1991.

We selected opioid concentrations for this study based on an approximately five- to sixfold relative potency of sufentanil to fentanyl when administered parenterally, ${ }^{13}$ although Coda et al. ${ }^{14}$ recently concluded that when given epidurally their relative potency may be closer to 3:1. Consideration also was given to limiting the total epidural sufentanil dose to the $30 \mu \mathrm{~g}$ previously shown to be safe for newborns. ${ }^{9}$ The greater bupivacaine concentration in the bolus in group B was selected to ensure adequate onset of analgesia.
In this study we found significant placental transfer of sufentanil and fentanyl after epidural administration during labor; sufentanil transfer appeared greater than that of fentanyl. The larger UV/MV ratio for sufentanil as compared with fentanyl ( 0.81 vs. $0.37 ; P=0.003$ ) may reflect the greater lipid solubility of sufentanil relative to that of fentanyl, as determined by their octanol: buffer distribution coefficients (fentanyl 955 and sufentanil 1,737 ). ${ }^{15}$ The degree of placental transfer of sufentanil in this study is greater than that reported by others. Kick et al., $\mathbb{\$}$ for example, were unable to detect sufentanil in neonatal plasma after epidural administration of $10-30 \mu \mathrm{~g}$ given for labor analgesia. The

Table 5. Plasma Bupivacaine Concentration

|  | Bupivacaine | Bupivacaine- <br> Fentanyl | Bupivacaine- <br> Sufentanil |
| :--- | :---: | :---: | :---: |
| UA bupivacaine $(\mathrm{ng} / \mathrm{ml})$ | $86 \pm 19$ | $137 \pm 29$ | $116 \pm 47$ |
| UV bupivacaine $(\mathrm{ng} / \mathrm{ml})$ | $77 \pm 19$ | $103 \pm 11$ | $148 \pm 27^{*}$ |
| MV bupivacaine $(\mathrm{ng} / \mathrm{ml})$ | $278 \pm 25$ | $306 \pm 74$ | $346 \pm 61$ |
| UV/MV ratio | 0.29 | 0.33 | 0.43 |

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Table 6. Maternal and Cord Plasma Opioid Concentration

| Fentanyl ( $\mathrm{ng} / \mathrm{ml}$ ) | $\begin{aligned} & \text { UV } \\ & (n=13) \end{aligned}$ | $\begin{gathered} \text { UA } \\ (\mathrm{n}=9) \end{gathered}$ | $\begin{gathered} M V \\ (n=13) \end{gathered}$ | $\begin{aligned} & U V / M V \\ & (n=13) \end{aligned}$ |
| :---: | :---: | :---: | :---: | :---: |
| Sufentanil ( $\mathrm{ng} / \mathrm{ml}$ ) | $0.18 \pm 0.03$ | $0.10 \pm 0.07$ | $0.52 \pm 0.03$ | $0.37 \pm 0.08$ |
|  | $\begin{gathered} \text { UV } \\ (\mathrm{n}=8) \end{gathered}$ | $\begin{gathered} \text { UA } \\ (n=5) \end{gathered}$ | $\begin{gathered} M V \\ (\mathrm{n}=8) \end{gathered}$ | $\begin{aligned} & \mathrm{UV} / \mathrm{MV} \\ & (\mathrm{n}=8) \end{aligned}$ |
|  | $0.016 \pm 0.002$ | $0.006 \pm 0.006^{*}$ | $0.019 \pm 0.005$ | $0.81 \pm 0.07 \dagger$ |
| UV = umbilical vein; $U A=$ umbilical artery; $M V=$ maternal vein. |  |  |  |  |
| - Value reflects sufentanil concentration detected in one sample. The four samples in which no sufentanil was detected were assigned a value of 0.0 for the calculation of the mean concentration. $\dagger P=0.003$ versus UV/MV ratio for fentanyl. |  |  |  |  |

plasma UV/MV ratio for sufentanil of 0.33 reported by Palot et al., \| also was much less than the 0.81 value we obtained. Steinberg et al. ${ }^{16}$ failed to detect sufentanil in $14(37 \%)$ of 38 UV samples after administration of sufentanil by an intermittent bolus technique for labor analgesia, whereas in the current study sufentanil was detected in all of the UV plasma samples obtained. These differences can be explained by the greater degree of sensitivity of our sufentanil assay, which had a lower limit of detection of $0.01 \mathrm{ng} / \mathrm{ml}$ compared with $0.02-0.05 \mathrm{ng} / \mathrm{ml}$ in the other studies cited. The UV/ MV ratio for sufentanil in our study is similar to that reported by Vertommen et al. ${ }^{17}$ when the opioid was administered epidurally in larger doses with bupivacaine for cesarean section. The significant correlation between MV and UV sufentanil concentrations in this study may reflect rapid placental diffusion of sufentanil as a result of its lipophilicity. There was no correlation between sufentanil UV concentrations and other factors such as total sufentanil dose or UV pH .
Highly lipophilic drugs have generally been considered to undergo more rapid placental ${ }^{18}$ and dural ${ }^{19}$ transfer than less lipophilic agents. However, some studies have shown that tissue permeability of spinal meninges ${ }^{20}$ or rabbit cornea ${ }^{21}$ has a biphasic relation; extremely hydrophilic and hydrophobic drugs had lower permeability coefficients than drugs of intermediate hydrophobicity. This may relate to layers of varying lipid and water content within these membranes resulting in rate-limiting steps with drugs at either extreme of solubility. ${ }^{20,22}$ Whether or not this is

[^5]applicable to placental transfer is unclear. In two in vitro studies of fentanyl ${ }^{23}$ and sufentanil ${ }^{24}$ in a perfused human placenta model, Zakowski et al. demonstrated rapid transfer of both fentanyl and sufentanil. Maternal-to-fetal clearance for fentanyl was somewhat greater than that for sufentanil; however, fetal-to-maternal clearance was greater with sufentanil, which also was sequestered in larger amounts within the placenta. ${ }^{24}$ In vivo, factors other than intrinsic tissue permeability assume importance. This is particularly true for lipophilic drugs, the transfer of which is strongly influenced by three factors: placental blood flow, which helps to maintain the concentration gradient; protein binding on either side of the placenta, which affects the gradient of the diffusible unbound drug; and the area available for drug diffusion. ${ }^{25}$


Fig. 2. The strong, significant correlation between maternal venous (MV) and umbilical venous (UV) sufentanil concentrations at the time of delivery. Fisher's $r$-to- $z$ correlation coefficient was $0.952 ; P<0.0001$.

Studies such as the current one are limited in that the UV／MV ratio describes only the relative concentrations of drug in the blood at one point in time（delivery）， which may not reflect the total amount of the drug in the neonate．Highly lipophilic drugs may well be se－ questered in the neonatal brain or other tissues．Indeed， the absence of sufentanil in most of the UA samples in the current study indicates neonatal tissue uptake of sufentanil and incomplete drug redistribution in the fetus at the time of delivery．We believe that clinically significant concentrations of sufentanil were unlikely to have been present in the neonatal brain at birth， given the vigorous behavior of these infants．However， in view of the degree of placental transfer of epidural sufentanil，it is conceivable that very large doses might result in neonatal depression．${ }^{10}$
One finding that is not easily explained is the greater UV $\mathrm{P}_{\mathrm{CO}_{2}}$ in group B －S compared with the other groups． This could reflect maternal opioid respiratory depres－ sion acutely increasing maternal arterial $\mathrm{P}_{\mathrm{CO}_{2}}$ with a resultant increase in UV $\mathrm{P}_{\mathrm{CO}_{2}}$ ，or decreased placental perfusion．Although there was no clinical evidence of respiratory depression in the mothers，maternal blood gas analyses were not available to confirm this．Exten－ sive clinical experience with epidural sufentanil given during labor suggests that maternal respiratory depres－ sion is an uncommon problem．The greater UV bupi－ vacaine concentrations in group B－S also are hard to explain，as total cumulative dosages of bupivacaine were similar in the three groups．It is tempting to relate the increased UV bupivacaine concentration in group B－S to the greater UV $\mathrm{P}_{\mathrm{CO}_{2}}$ in this group．Although UV $p \mathrm{H}$ was not statistically different among the groups and all values were within the normal range，the mean UV $p \mathrm{H}$ was lower in group $\mathrm{B}-\mathrm{S}$ than in groups B－F and B．A mild respiratory acidosis and slightly elevated UV $p \mathrm{H}$ are common in healthy newborns and may result from numerous factors including maternal hypotension or aortocaval compression，a prolonged second stage with vigorous maternal expulsive efforts，${ }^{26.27}$ decreased pla－ cental perfusion，and umbilical cord compression．De－ creased fetal $p \mathrm{H}$ and acidosis can result in greater bu－ pivacaine concentrations as a result of several mecha－ nisms，including ion trapping（an increase in the un－ionized drug fraction on the fetal side of the pla－ centa，which decreases fetal－maternal bupivacaine transfer）${ }^{28}$ ；increased maternal－fetal drug clearance due to an increased gradient of un－ionized drug ${ }^{29}$ ； changes in protein binding，which may affect the gra－ dient of un－ionized drug；and changes in fetal drug
clearance or tissue distribution．In a study in pregnant rabbits，Gaylard et al．${ }^{25}$ also found that bupivacaine underwent increased placental transfer during a period of maternal hypoperfusion，perhaps because of mobi－ lization of drug stored within the placenta．Thus，al－ though the difference in UV $p \mathrm{H}$ between the B－S and other groups was small，in conjunction with factors that affect placental perfusion（e．g．，maternal aortocaval compression）it may have influenced bupivacaine transfer．An alternative and more likely explanation is that the greater UV bupivacaine concentration in group B－S merely reflected the somewhat greater MV value in this group．Despite small differences among the groups， bupivacaine concentrations in group B－S neonates were low and not a cause for concern，particularly because bupivacaine is free of neurobehavioral effects．${ }^{30}$ Newer techniques using more dilute bupivacaine infus－ ions should result in even lower neonatal concentra－ tions．
Although substantial placental transfer of both opioids occurred，absolute levels were low and there were no differences in Apgar scores，time to sustained respiration，or NACS at the time of delivery when com－ pared with the control group．Although neonates in all groups had comparable NACS at 2 h ，the NACS at 24 h in group B－F were significantly lower than those in the other groups．The composite scores for groups B－S and B newborns reflect the usual improvement seen over the first 24 h ，whereas those for group B－F newborns did not improve during this period．Although the num－ bers in this study are small，they should be sufficient to detect a statistically significant difference in NACS of 1.5 points among the groups with a power of 0.8 and $95 \%$ confidence．Helbo－Hansen et al．${ }^{31}$ also re－ ported lower NACS scores in certain categories at 2 and 24 h in newborns delivered by cesarean section using epidural anesthesia with fentanyl（ $50-100 \mu \mathrm{~g}$ ）and bu－ pivacaine．The lower NACS at 24 h in group B－F may relate to a longer elimination half－life for fentanyl re－ sulting in a persistent，mild depressant effect．Phar－ macokinetic studies of fentanyl in newborns have shown that clearance is low in the early neonatal pe－ riod，perhaps as a result of immature liver enzyme sys－ tems．${ }^{32}$ As newborn blood samples were not obtained in the current study，it was not possible to correlate opioid plasma concentrations at 24 h with neurobe－ havioral scores．
Why were neurobehavioral effects greater with fen－ tanyl when UV／MV drug ratios were greater with su－ fentanil？This apparent paradox can partly be explained

[^6]by dififerences in maternal upt： hough we administered fentan nutio of $5.7: 1$ ，the ratio of fenta smples was $27: 1$ ，an almost fi
elative concentration of relative concentration of fenta probably reflects greater matern than of fentanyl，resulting in esposure to sufentanil．UV suf
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iv samples of $11: 1$ suifunanil that crosseses andinnil that crosses theop raions perfusing the dosess giv od lower than the placenta dsorption of sufe centa，and greater fetan
chan sufentanil ${ }^{2,24}$ greater fetarthe oncentrations and furthe ${ }_{\delta}^{\text {F }}$ expl ofentanil．Despite our finêting the differences in NAC虂 ind deperssion with fentanyl写hat prricularly considering tel at se BF newborns had a NACsigreat date，no adverse long termeêeffec mith transient drug－relategd ne sion．${ }^{334}$ Despite this，the ${ }^{\text {Gidmandm }}$ atics Committee on Dru⿳⿵冂𠃍冖口⿱⺈⿻コ一心⿴⿱冂一⿰丨丨夕刂灬 h during labor，drugs be used th onthe neonate，as determi ${ }^{\text {ha }}$ ed $b$ ing．${ }^{3 .}$ Our findings with $\stackrel{\xi}{8}^{\circ}$ ufen others $\}$ who have similad ly fo nual neurobehavior with doses icrumstance．
In summary，the anesthèㅡtic ts sudyall provided adequaee ana lirery with no severe side offect Howerer，given the small $\vec{p}$ umb pasible to draw firm concelesion ineficicacy or side effects in ith Phacental transfer of both sufenta when these drugs are administer nalgesia．Although placental tr： paras to be greater than that of $f$ Mrelaled with maternal conc Uuemal sufentanil uptake may anciated with lower neurobe 4h of life，although none of $t$ ally significant depression．Alt
acpable for use with epidur 4alsiolology，V83，No 2，Aug 1995

PLACENTAL TRANSFER OF EPIDURAL OPIOIDS DURING LABOR
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by differences in maternal uptake of the opioids. Although we administered fentanyl and sufentanil in a ratio of 5.7:1, the ratio of fentanyl to sufentanil in MV samples was $27: 1$, an almost fivefold increase in the relative concentration of fentanyl to sufentanil. This probably reflects greater maternal uptake of sufentanil than of fentanyl, resulting in relatively less neonatal exposure to sufentanil. UV sufentanil levels were extremely low, with a ratio of fentanyl to sufentanil in UV samples of $11: 1$. Restated simply, the amount of sufentanil that crosses the placenta is insignificant because, relative to the doses given, sufentanil concentrations perfusing the placenta are approximately fivefold lower than those of fentanyl. In addition, greater absorption of sufentanil than of fentanyl by the placenta, and greater fetal-to-maternal clearance of sufentanil ${ }^{23,24}$ may further explain the lower neonatal concentrations and lack of neurobehavioral effects with sufentanil. Despite our findings, we do not believe that the differences in NACS indicate neurobehavioral depression with fentanyl that is of clinical concern, particularly considering that seventy percent of group B-F newborns had a NACS greater than 35 at 24 h . To date, no adverse long term effects have been associated with transient drug-related neurobehavioral depression. ${ }^{33.34}$ Despite this, the American Academy of Pediatrics Committee on Drugs has recommended that, during labor, drugs be used that have the least effect on the neonate, as determined by neurobehavioral testing. ${ }^{35}$ Our findings with sufentanil confirm those of others ${ }^{4} \mathbb{S}$ who have similarly found no effect on neonatal neurobehavior with doses less than $30 \mu \mathrm{~g}$ in this circumstance
In summary, the anesthetic techniques used in this study all provided adequate analgesia for labor and delivery with no severe side effects in any of the groups. However, given the small number of patients, it is not possible to draw firm conclusions regarding differences in efficacy or side effects with these three regimens. Placental transfer of both sufentanil and fentanyl occurs when these drugs are administered epidurally for labor analgesia. Although placental transfer of sufentanil appears to be greater than that of fentanyl and is strongly correlated with maternal concentrations, significant maternal sufentanil uptake may considerably reduce neonatal opioid exposure. Fentanyl administration was associated with lower neurobehavioral test scores at 24 h of life, although none of the newborns had clinically significant depression. Although both drugs are acceptable for use with epidural bupivacaine during
labor, the reduced neonatal opioid exposure with sufentanil suggests that it may have some advantages over fentanyl.

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[^1]:    $P=0.03$（ $B-S$ vs．$B$ and $B-F)$ ．

[^2]:    NACS = neurologic and adaptive capacity score.

    * $P=0.02$ (B-F vs. $B$ and $B-S$ ).

[^3]:    Anesthesiology, V 83, No 2, Aug 1995

[^4]:    $U A=$ umbilical artery; $U V=$ umbilical vein; $M V=$ maternal vein.

    - $P=0.04$ (B-S vs. $B-F)$ and $P=0.003$ (B-S vs. $B$ ).

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