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Effect of Epidural Fentanyl on Neonatal Respiration

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Background: **The addition of opioids to epidural infusions for laboring mothers may reintroduce the problem of neonatal depression seen with systemic opioids. The authors studied neonatal respiration and neurobehavior in newborns of mothers randomized to receive epidural analgesia with or without fentanyl.**

Methods: **One hundred thirty-eight women in labor received loading doses of plain bupivacaine. When pain-free, they received an infusion of either 0.125% bupivacaine alone or 0.0625% bupivacaine with 2.5 μg/ml fentanyl. After delivery, transcutaneous oxygen tension and carbon dioxide tension were recorded in the newborns every 10 s until 90 min after delivery using a transcutaneous oxygen–carbon dioxide monitor. Umbilical venous and arterial acid-base status, Apgar scores, and Neurologic and Adaptive Capacity Scores 2 h and 24 h after delivery were measured. The umbilical venous plasma fentanyl concentration was correlated with indices of neonatal respiration and welfare in the fentanyl group.**

Results: **One hundred fourteen newborns delivered vaginally were studied. In the fentanyl group, the mean (range) maternal dose of fentanyl was 184 μg (range, 53–400), and the umbilical venous fentanyl concentration was 0.077 ng/ml (range, <0.021 to 0.244). There were no significant differences between the groups for any indices of neonatal respiration or neonatal welfare, and the plasma fentanyl concentration did not correlate with any of these indices.**

Conclusions: **The results suggest that fentanyl added to epidural bupivacaine infusions during labor does not depress neonatal respiration or adversely affect neurobehavioral scores and other indices of neonatal welfare. (Key words: Labor; newborn; opioids; placental transfer; transcutaneous oxygen and carbon dioxide.)**

SYSTEMIC opioids given to mothers in labor cause many adverse neonatal effects, including respiratory depression.[1] Epidural analgesia using bupivacaine alone is usually associated with better neurobehavioral scores[2] and less neonatal respiratory depression[3] than is systemic opioid analgesia. Since 1980, epidural opioids have been used increasingly. They allow a reduction in the dose of local anesthetic without compromising analgesia, resulting in less motor blockade and greater maternal mobility and satisfaction.[4,5] However, use of opioids *via* the epidural route may reintroduce the problem of neonatal depression seen with systemic opioids. Until now, randomized studies comparing infusions of bupivacaine alone with those containing reasonable doses of opioids have detected no neonatal detriment.[5–7] They have, however, used only conventional indices of neonatal welfare such as the Neurologic and Adaptive Capacity Score, the Apgar score, and umbilical cord acid-base and respiratory gas status, tests that may not detect minor degrees of neonatal respiratory depression. This prospective, randomized study was designed to determine whether the addition of fentanyl to an epidural infusion of bupivacaine for pain relief in labor affects neonatal respiration compared with infusions of bupivacaine alone, by examining neonatal transcutaneous carbon dioxide and oxygen tensions (PCO_2 and PO_2, respectively) as well as the usual methods of neonatal assessment.

Methods

After ethics committee approval, we recruited 138 women who weighed <110 kg with a singleton fetus of cephalic presentation and at least 36 weeks' gestation and who requested epidural analgesia for labor pain. Any woman with a history of diabetes mellitus or preeclampsia or who had received systemic opioids earlier in labor was excluded. All received a test dose of 10 mg bupivacaine followed by a loading dose of 8–10 ml

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0.25% bupivacaine. Supplementary doses of 5 ml 0.25% bupivacaine were given if required to achieve satisfactory analgesia. When the mothers were pain-free, their written consent was obtained and they were randomly assigned, using opaque sealed envelopes, to receive an infusion of either 0.125% bupivacaine alone (controls) or 0.0625% bupivacaine with 2.5 μg/ml fentanyl (the fentanyl group). The women, their midwives, and physicians were blinded to the treatment group. The infusion rate was adjusted to maintain analgesia and a sensory level at T8-T10. Hourly verbal numeric pain scores, on a scale of 0-10, were recorded throughout labor, and breakthrough pain was treated with bolus doses of 5 ml 0.25% bupivacaine in both groups.

Assessment of Neonatal Welfare

Apgar scores were recorded 1 and 5 min after delivery. At the time of delivery the umbilical cord was double clamped. Umbilical arterial and venous blood samples were drawn into heparinized syringes to measure acid-base and gas status. At 2 h and 24 h after delivery, neonatal neurobehavior was assessed using the Neurologic and Adaptive Capacity Score as described by Amiel-Tison *et al.*[8] The state of alertness of each newborn was noted during the 90-min study period. Four states were recorded: awake and quiet, awake and crying, feeding, and asleep.

Measurement of Transcutaneous Gas Tensions

Immediately before delivery of the baby, a combined transcutaneous oxygen and carbon dioxide monitor (Novametrix model 840-VFD, Wallingford, CT) was calibrated *in vitro*. As soon as possible after delivery, the skin on the newborn's chest was cleaned with alcohol and dried, and the probe was attached to the right side of the chest. The sensor temperature was set to 44°C. Ten minutes were allowed for the transcutaneous PCO_2 ($tcPCO_2$) sensor to equilibrate, and 15 min were allowed for the transcutaneous PO_2 ($tcPO_2$) sensor, after which $tcPCO_2$ and $tcPO_2$ were recorded manually every 10 s until 90 min after delivery. Trend data of $tcPCO_2$ and $tcPO_2$ were downloaded onto the spreadsheet software package Excel (Microsoft, Redmond, WA) on an IBM-compatible personal computer.

Assessment of Neonatal Respiration

For each newborn, mean values per minute were calculated, and graphs of $tcPO_2$ and $tcPCO_2$ against time were plotted (fig 1). For each graph, a line of best fit was drawn, from which the slope and y intercepts were obtained. Mean (SD) slopes and mean (SD) intercepts were calculated. Mean (SD) $tcPO_2$ and $tcPCO_2$ were also calculated from absolute values 20 and 90 min after delivery.

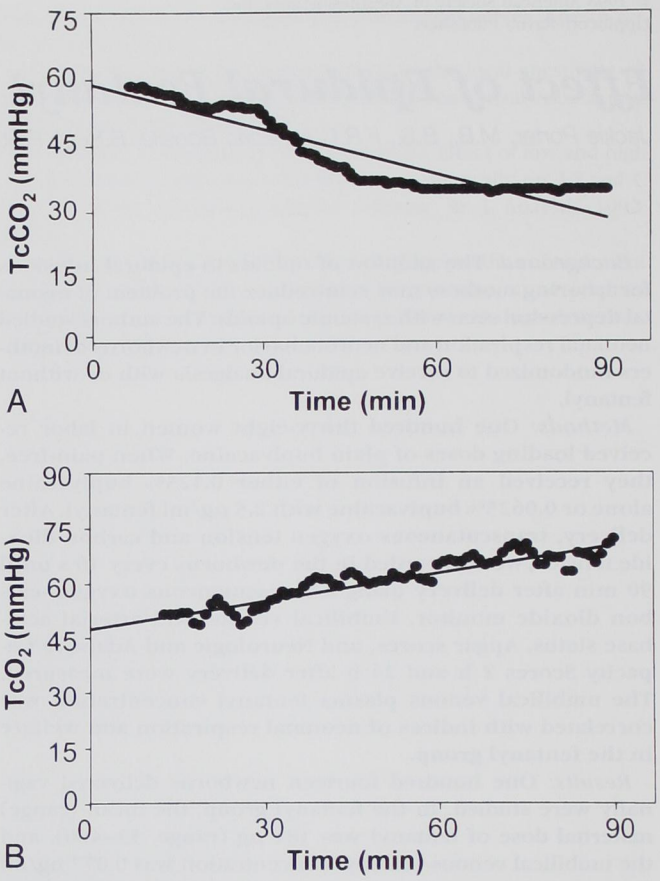

Fig. 1. Transcutaneous respiratory carbon dioxide (*A*) and oxygen (*B*) tensions recorded in one newborn and plotted against time, with lines of best fit (gradient).

Plasma Drug Assays

In the fentanyl group, part of each umbilical venous blood sample was set aside for fentanyl assay. The samples were centrifuged and the separated serum stored at −20°C. Subsequently plasma fentanyl concentrations were measured using a Coat-A-Count fentanyl solid-phase ^{125}I radioimmunoassay (EURO/DPC Ltd, Gwynedd, Cymru, UK), as previously described.[9] In a random subset of mothers and newborns, plasma bupivacaine concentrations were measured at delivery by gas-liquid chromatography, as previously described,[10] using 3%OV17 as the stationary phase.

Table 1. Demographic Data

	Controls (n = 70)	Fentanyl (n = 68)
Mean (SD)		
Age (yrs)	28.5 (5.4)	27.9 (5.4)
Maternal weight (kg)	77.4 (12.4)	76.3 (10.3)
Neonatal weight (kg)	3.4 (0.5)	3.5 (0.5)
Duration of infusion (min)	356 (164)	380 (199)
Duration of labor (min)	705 (303)	718 (253)
Mode of delivery [no. (%)]		
SVD	27 (38)	24 (36)
Instrumental	33 (47)	30 (45)
Cesarean	10 (14)	13 (19)

SVD = spontaneous vaginal delivery.

Statistical Analysis

Student's *t* test was used to compare maternal age and weight and indices of neonatal respiration (20- and 90-min gas tensions, slopes and intercepts of gas tensions) between the two groups. The Mann-Whitney U test was used for nonparametric comparisons except for comparisons of parity, delivery type, and low Neurologic and Adaptive Capacity Scores when the chi-square test was used. Pearson's correlation was used to correlate umbilical venous fentanyl concentration in the fentanyl group with maternal plasma fentanyl concentration, and with indices of neonatal respiration and welfare. Linear regression was used to relate maternal plasma fentanyl concentration to the total dose of fentanyl.

Results

One hundred thirty-eight women were recruited to the study, 68 in the fentanyl group and 70 as control subjects. Ten control newborns and 13 in the fentanyl group were delivered by cesarean section and were not studied. One newborn was withdrawn early in the study period at the request of the mother. This left 60 newborns in the control group and 54 in the fentanyl group.

Table 1 shows demographic data. Maternal age, maternal and neonatal weights, duration of labor and epidural analgesia, and mode of delivery were similar in the two groups. As infusion rates were adjusted to maintain analgesia and a stable sensory level, median pain scores were zero, with no significant difference between treatment groups. Table 2 shows data for umbilical arterial and venous acid-base and respiratory gas status, Apgar scores, and Neurologic and Adaptive Capacity Scores. There were no significant differences between the two groups for any of the indices examined. The time spent in each of the four states of alertness were similar in the two groups.

Figure 1 shows an example of the changes in transcutaneous respiratory gas tension in one newborn. Figures 2 and 3 are composite graphs showing the lines of best fit for all the newborns from graphs of $tcPO_2$ and $tcPCO_2$ against time. There were no significant differences between the two groups for any of the indices of neonatal respiration shown in table 3.

Table 4 shows the mean doses of fentanyl and bupivacaine in the two groups. The fentanyl assay was able to detect as little as 0.021 ng/ml, and coefficients of variation ranged from 1.46% to 2.36%. The intrapair correlation coefficient for duplicate samples was 0.88. We could not measure plasma fentanyl concentrations universally, but as many as possible of the umbilical venous samples were included, because this was the main purpose of the study. Table 4 shows maternal and umbilical venous concentrations of fentanyl and bupivacaine. The umbilical venous fentanyl concentration did not correlate significantly with any of the indices of neonatal respiration or welfare. The diminution in bupivacaine dose requirement made possible by the addition of fentanyl resulted in an umbilical venous bup-

Table 2. Indices of Neonatal Welfare

	Controls (n = 60)	Fentanyl (n = 54)
UA		
pH	7.28 (7.1–7.35)	7.22 (7.09–7.32)
PO_2 (kPa)	1.7 (0.7–3.3)	2.10 (1.0–4.3)
Base excess (mM)	−6.7 (−2.7 to −16.5)	−7.6 (−2.0 to −18.3)
UV		
pH	7.35 (7.12–7.45)	7.29 (7.18–7.41)
PO_2 (kPa)	3.4 (2.0–6.3)	3.8 (1.9–5.6)
Base excess (mM)	−7.5 (−1.8 to −12.0)	−7.7 (−1.8 to −13.1)
Apgar score		
1 min	9 (1–10)	9 (3–10)
5 min	10 (6–10)	10 (8–10)
NACS 2 h	36 (32–38) (n = 56)	35 (29–39) (n = 50)
NACS 24 h	37 (33–39) (n = 50)	37 (31–39) (n = 48)
NACS <35		
2 h	7/56	9/50
24 h	3/50	6/48

NACS = neurologic and adaptive capacity score.
Values are median (range) or numbers.

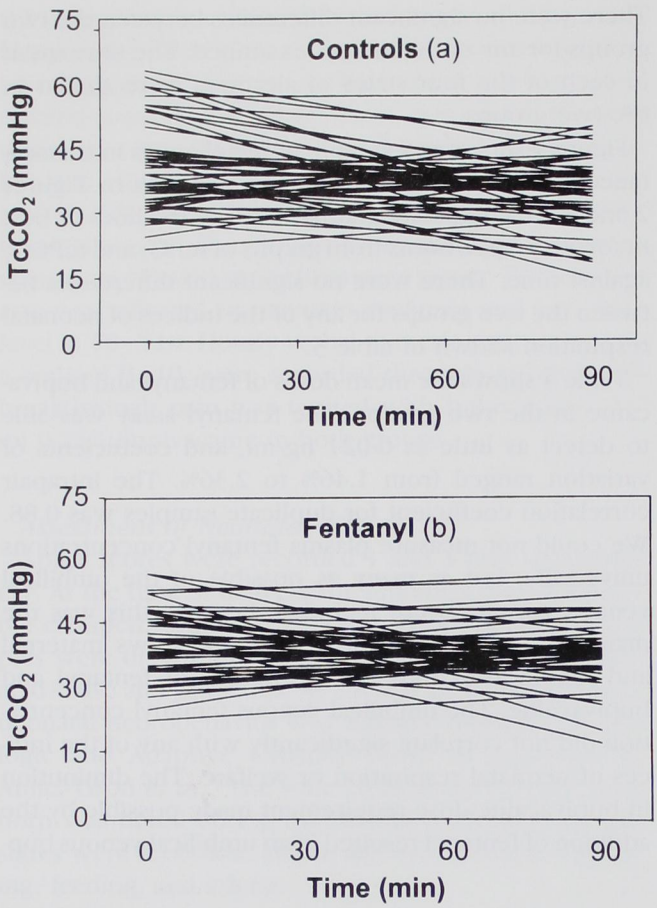

Fig. 2. Gradients (derived as in fig. 1) for transcutaneous carbon dioxide tensions plotted against time for all newborns.

ivacaine concentration in the fentanyl group of less than half that in the control group.

Discussion

Transcutaneous gas measurement provides noninvasive and continuous monitoring of respiratory gas status.[11] Many studies have shown good correlation and equivalence between transcutaneous gas tensions and arterial blood values in newborns and infants for both transcutaneous oxygen and carbon dioxide, particularly when the probe temperature is ≥44°C.[12–14] This mode of measurement is at its most accurate in the newborn, before skin changes reduce the correlation with arterial values.[15] Therefore it is well suited to measure newborn respiratory changes, which occur most rapidly during the first hour of life.[16] The slow response time was no disadvantage to our aim, which was to examine trends in gas tensions rather than rapid changes. To allow time for the skin to arterialize, we delayed collection of transcutaneous carbon dioxide data for 10 min and transcutaneous oxygen data for 15 min after application of the probe. The state of alertness has been shown to affect neonatal breathing pattern and oxygenation.[17,18] However, the two groups in our study spent similar time periods in each of the four states recorded.

Although pulse oximetry may be useful in various clinical settings, there would have been several disadvantages to its use in our study. First, the oxygen level is a less-sensitive indicator of opioid-induced respiratory depression than is the carbon dioxide level. Second, hemoglobin oxygen saturation not only has a sigmoid relation with the partial pressure of arterial oxygen but the position of the oxygen dissociation curve itself is affected by the concentration of fetal hemoglobin, neonatal acidosis, and the partial pressure of arterial carbon

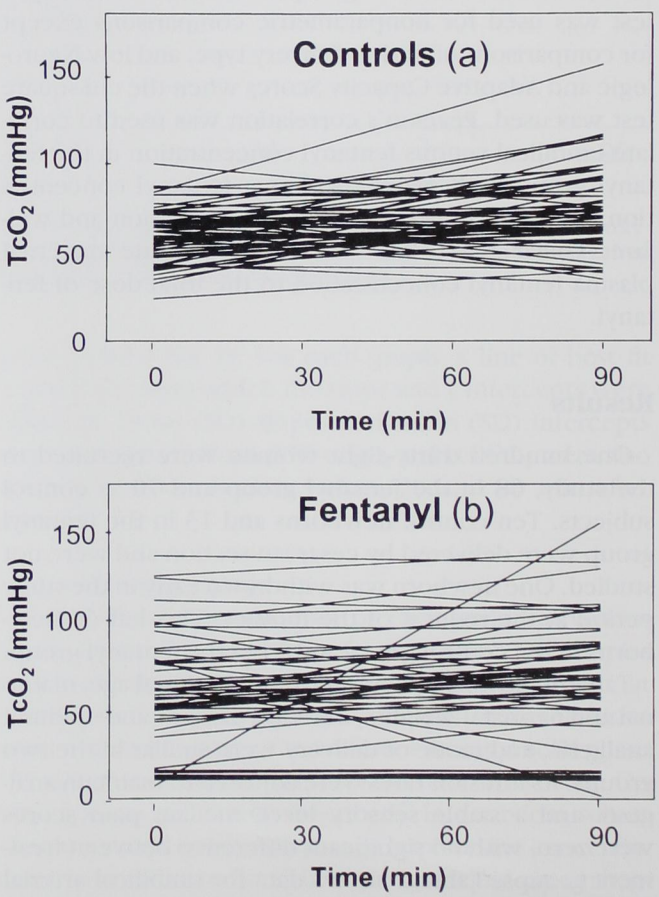

Fig. 3. Gradients (derived as in fig. 1) for transcutaneous oxygen tension plotted against time for all newborns.

Table 3. Neonatal Respiratory Gas Status

	tcP_{CO_2}		tcP_{O_2}	
	Controls (n = 60)	Fentanyl (n = 54)	Controls (n = 60)	Fentanyl (n = 54)
Intercept (mmHg)	39 (11.25)	37.5 (8.25)	62.25 (15.75)	60 (19.5)
(kPa)	5.2 (1.5)	5.0 (1.1)	8.3 (2.1)	8.0 (2.6)
Gradient (mmHg/h)	−0.525 (0.97)	−0.225 (1.125)	1.05 (2.025)	0.6 (2.475)
(kPa/h)	−0.07 (0.13)	−0.03 (0.15)	0.14 (0.27)	0.08 (0.33)
20 min (mmHg)	39 (9.0)	38.25 (6.0)	63.75 (14.25)	59.25 (14.25)
(kPa)	5.2 (1.2)	5.1 (0.8)	8.5 (1.9)	7.9 (1.9)
90 min (mmHg)	37.5 (6.0)	38.25 (6.0)	68.25 (21.75)	63.75 (15.0)
(kPa)	5.0 (0.8)	5.1 (0.8)	9.1 (2.9)	8.5 (2.0)

Values are mean (SD).

dioxide. Third, poor peripheral perfusion may make pulse oximetry recording inaccurate during the first 24 h of life.[19] Fourth, while the ductus remains open, saturation varies with sampling site.[19,20] Fifth, the pulse oximeter is prone to movement artifact, a particular problem in the newborn during the first 1–3 h.[19,21,22] Therefore, we selected transcutaneous gas tensions for this study and have assessed the rate of change of respiratory gas tensions (*i.e.*, the gradient) as an index of the rate at which neonatal respiration adapts.

Our results suggest that fentanyl added to epidural bupivacaine infusions during labor had little effect on neonatal respiration. This may be because either measurement of $tcPO_2$ and $tcPCO_2$ is not sufficiently sensitive or the concentrations of fentanyl in the newborn were too low to cause an effect. The absence of any correlation between plasma fentanyl concentration in the cord and any aspect of neonatal welfare argues against a pharmacologic effect from these concentrations. Although the ventilatory response to carbon dioxide might be a more sensitive index, a shift would not necessarily affect basal ventilation, although it may affect the ability of the respiratory center to respond to an increased ventilatory demand.

Although there was a declining gradient in $tcPCO_2$ over time, which was slower in the fentanyl group, there was a large variation between the babies with no significant difference between mean gradients or intercepts in the two groups. Similarly, there was a trend toward an increase in $tcPO_2$ over time, which was greater in the control group, but again the difference between the groups was not statistically significant. A valid power calculation was impossible at the start of the study, because transcutaneous respiratory gas measurement had not previously been used to assess the respiratory effects of epidural opioids in the newborn. To detect a significant difference in the gradient for carbon dioxide over time with 80%

Table 4. Pharmacokinetic Data

	Controls (n = 70)	Fentanyl Group (n = 68)	
	Bupivacaine Data	Bupivacaine Data	Fentanyl Data
Maternal dose	132 (53) mg	99 (43) mg	183 (75) μg
Maternal plasma concentration	0.497 (0.174) μg/ml (n = 28)	0.251 (0.143) μg/ml (n = 33)	0.226 (0.115) ng/ml (n = 29)
UV plasma concentration	0.197 (0.097) μg/ml (n = 31)	0.091 (0.040) μg/ml (n = 46)	0.077 (0.061) ng/ml (n = 48)

Values are mean (SD).

power at the 5% level would have required 193 newborns per group. The equivalent number from the oxygen data would be 395 newborns per group. This suggests a potential difference that would not be clinically important.

What level of fentanyl would produce respiratory depression in the newborn? Cartwright *et al.*[23] found that a fentanyl concentration of 2 to 3.1 ng/ml was required to produce 50% depression of carbon dioxide responsiveness in adults after general anesthesia for peripheral arterial surgery. Stoeckel *et al.*,[24] in a study using adult volunteers, found that plasma fentanyl concentrations of $\geq$3 ng/ml were associated with 50% depression of the ventilatory response to carbon dioxide. Similar studies have not been performed in newborns. However, fentanyl is largely albumin bound, and fetal:maternal ratios after use in labor are frequently about 1.0 for total drug and slightly higher for free drug.[25-27] Early studies on the effects of morphine suggest that the fetus may be more susceptible than the adult to opioid effects.[28] More recently, some investigators have postulated extreme sensitivity of the newborn to the respiratory effects of fentanyl,[29] whereas others suggest that the susceptibility of infants to postoperative apnea is similar to that in adults.[30] After major surgery during which large doses of fentanyl were used, newborns were extubated when mean plasma fentanyl concentrations were 0.05 to 0.77 ng/ml,[29] whereas the maximum concentration measured in our study was 0.24 ng/ml.

Our study, like that of Fernando *et al.*,[27] revealed no correlation between cord fentanyl concentrations and Apgar or neurobehavioral score. Loftus *et al.*[31] compared placental transfer and neonatal neurobehavioral effects of fentanyl and sufentanil given epidurally by bolus and infusion for labor analgesia in a dose ratio of 5.7:1. The latter drug is given in so low a dose that it usually defies measurement in cord blood. This was not so in our study. At delivery, umbilical:maternal venous plasma concentration ratios were higher for sufentanil than for fentanyl, results that were at variance with those of other investigators and with predictions based on the high binding of sufentanil to α_1-acid glycoprotein.[32] In the study by Loftus *et al.*,[31] the use of epidural sufentanil was associated with funic acidosis and increased cord bupivacaine concentration. Nevertheless, fetal exposure to fentanyl was higher, and in the fentanyl group neurobehavioral scores did not show the expected improvement by 24 h, reflecting its prolonged half-life and the potential for unbinding of the albumin-bound load in the first day of life.[33]

Epidural fentanyl might also have an indirect effect on fetal welfare, given that it has been shown to increase the incidence of episodes of maternal hemoglobin desaturation, particularly in the second stage of labor.[9,34] However, no correlation was found in these studies between the incidence of maternal desaturation and any index of neonatal welfare.

Our results show an upward trend in $tcPO_2$ in both groups until 1.5 h of life. This corresponds with the results of previous studies that examined the normal values for respiratory gases immediately after birth.[16,35,36] The PaO_2 value in neonatal arterial blood varies[16] and is much lower in neonates than in adults because of perfusion of underventilated alveoli and shunting across the ductus arteriosus and foramen ovale. The $PaCO_2$ value remains at about 4.6 kPa for at least 1 week,[37] compared with 5.1 kPa in the adult. The carbon dioxide levels we found during the first 1.5 h were higher than this in both groups. There was a trend toward a gradual decline, but no difference between the groups was detected.

In conclusion, we found no evidence of clinically important respiratory depression in the newborns of these mothers who had been given epidural infusions of fentanyl in doses up to 400 μg.

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