

Fetal Plasma Concentrations after Intraamniotic Sufentanil in Chronically Instrumented Pregnant Sheep

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Background: **Rapid progress is being made in fetal surgery. Because the fetus is capable of pain perception after the 26th week of gestation, adequate postoperative fetal pain management is essential. The preferred approach would provide fetal analgesia without affecting the mother. Intraamniotically administered sufentanil may be an interesting option if it achieves therapeutic plasma concentrations (PCs) in the fetus but not the mother.**

Methods: **After approval of the study, 25 or 50 μg sufentanil was administered intraamniotically in 10 chronically instrumented pregnant ewes. Maternal and fetal vital signs, arterial blood gases, and uterine blood flow were recorded over 120 min. Sufentanil PCs were determined before and 1, 3, 5, 10, 15, 30, 45, 60, 90, and 120 min after injection. Statistical analysis was performed using one- or two-way analysis of variance followed by Dunnett or Tukey test, as appropriate ($P < 0.05$; data presented as median [95% confidence interval]).**

Results: **After 25 μg sufentanil, fetal PC stabilized at 134 ± 89 pg/ml (after 10 min), and maternal PCs stabilized at 44 ± 11 pg/ml (after 15 min). After 50 μg sufentanil, fetal PCs stabilized at 134 ± 35 pg/ml (after 15 min), and maternal PCs reached 80 ± 25 pg/ml (at 30 min). Injection of 25 μg sufentanil intraamniotically did not affect maternal or fetal hemodynamics, uterine blood flow, or arterial blood gases. Fetal heart rate increased after administration of 50 μg sufentanil (maximum change at 10 min: +16 ± 12%).**

Conclusion: **The sheep fetus absorbs sufentanil after intraamniotic instillation. Significantly greater PCs were obtained in the fetal lamb as compared with the ewe. This suggests that investigation of intraamniotic opioids for fetal analgesia might be worthwhile.**

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BECAUSE of a rapid increase in diagnostic and therapeutic options, life-threatening fetal malformations, or those that have a devastating outcome if treatment is postponed until after birth, are now accessible to treat *in utero*.[1,2] Animal data and first case reports show promising results in treating, for instance, certain congenital heart diseases,[3,4] twin-reversed arterial perfusion,[5–7] diaphragmatic hernias,[8–10] bronchopulmonary malformations,[11] urinary tract obstruction,[12,13] and myelomenigoceles.[14]

Fetal analgesia has become a major issue in fetal surgery since it was shown that noxious stimuli are transmitted as early as the 26th gestational week.[15] However, adequate fetal postoperative analgesia cannot be achieved easily. Use of fetal local or regional anesthesia has not been described. Intravenous administration of analgesics to the mother in concentrations required to achieve adequate fetal plasma concentrations risks undesired maternal side effects. This is of particular concern because only the fetus, and not the mother, needs the drug. Although direct intramuscular or intravenous administration of opioids to the fetus is in routine use in some centers, it potentially risks bleeding as well as cord tamponade and arterial spasm.

Because access to the amniotic cavity is already established through the surgical intervention, analgesics might be administered into the amniotic fluid. This would expose primarily the fetus to the drug. Previous experimental and clinical studies have shown that intraamniotically applied digoxin,[16] vasopressin,[17] steroids,[18] or thyroxine[19] is absorbed by the fetus. However, it is not known whether administration of analgesics using this technique leads to appreciable blood concentrations in the fetus or whether measurable blood concentrations are built up in the mother.

We hypothesized that intraamniotically applied analgesics induce greater blood concentrations in the fetus than in the mother. To test our hypothesis, we determined fetal and maternal sufentanil plasma concentrations after intraamniotic administration of sufentanil in chronically instrumented pregnant sheep. This established model allows continuous monitoring and plasma sampling in an awake animal (*i.e.*, no interference with anesthetics). We used sufentanil in our study because it is a highly lipid-soluble compound, suggesting easy passage through fetal skin (or gastrointestinal tract) and transmembranous absorption. As an additional benefit, sufentanil passes the placental barrier to a lesser extent than does fentanyl.[20–22] Our findings indicate that intraamniotically applied sufentanil results in substantial

plasma concentrations in the fetus, whereas maternal plasma concentrations remain low.

Materials and Methods

Experimental Animals and Instrumentation

The study protocol was approved by the local committee on animal research of the University of Münster and follows the guidelines for the provision of standard care to laboratory animals. We studied 10 time-bred pregnant ewes weighing between 56 and 80 kg (mean, 66.2 ± 8.5 kg) with a mean gestational age of 120 days (range, 118–122 days; term average, 145 days).

Mother and fetus were instrumented as described previously.[21] Briefly, polyvinyl catheters were placed under general anesthesia into the maternal external jugular vein and carotid artery as well as into the fetal caval vein and aortic artery *via* the tibial vein and artery. A well-fitting 20-MHz pulsed Doppler flow probe (Baylor College of Medicine, Houston, TX; ID 4.0–6.0 mm) was secured around a branch of the uterine artery supplying the pregnant horn of the uterus and used for measurement of uterine blood flow. An additional catheter was placed in the amniotic fluid cavity and secured to a fetal hind limb for drug administration and amniotic pressure measurements. Estimated intraoperative amniotic fluid loss was replaced with warmed sterile saline, the uterus was closed, and all catheters were tunneled subcutaneously. Catheters were irrigated daily with sterile heparinized saline; animals were allowed free access to water and standard sheep food and received prophylactic antibiotics (cefamandole, gentamicin) daily.

Maternal mean arterial pressure, maternal heart rate, amniotic fluid pressure, fetal mean arterial pressure, and fetal heart rate were measured using a disposable strain gauge (Eco Trans DPT-7003; pvb Medizintechnik, Kirchseeon, Germany). Fetal mean arterial pressure was adjusted by subtracting amniotic fluid pressure. Uterine blood flow data were represented as kHz Doppler shift. Arterial blood samples for maternal and fetal blood gases as well as acid–base status were processed immediately after sampling (ABL 505; Radiometer, Copenhagen, Denmark) and corrected for maternal temperature (39°C; normal temperature for sheep). The blood gas analyzer was calibrated daily with reference liquid samples (Multicheck; Radiometer).

Experimental Design

The animals were studied in standing position in a study trolley. Each experiment was preceded by a period of 30 min, during which baseline hemodynamic conditions were obtained. We studied two sufentanil treatments: 25 and 50 μg intraamniotically. A time period of at least 48 h separated each treatment, and each animal received each treatment, in randomized order, thereby acting as its own control. We did not include a control group because the repeated fetal blood sampling might adversely affect fetal status.

Maternal mean arterial blood pressure, maternal heart rate, amniotic fluid pressure, fetal mean arterial blood pressure, and fetal heart rate were recorded before and 1, 3, 5, 10, 15, 30, 45, 60, 90, and 120 min after injection of the test compound. Venous blood samples (2 ml each) for determination of fetal and maternal sufentanil plasma concentrations were drawn at the same time. Associated blood loss was replaced with 2 ml saline. After centrifugation (1,500*g*, 10 min), plasma samples were kept frozen at −20°C until analysis. Maternal and fetal arterial blood gases and acid–base status were determined before and 5, 15, 30, 60, 90, and 120 min after drug administration. Animals were euthanized with propofol and potassium chloride after the final experiment, and fetal body weight was obtained. Mean fetal body weight at autopsy varied between 2.5 and 5.0 kg (mean, 3.35 ± 0.7 kg), resulting in dosages of 7.5 and 15.0 μg/kg sufentanil, respectively.

Sufentanil Concentration Assay

Sufentanil dihydrogen citrate was obtained from Janssen-Cilag, Neuss, Germany. Fetal and maternal sufentanil plasma concentrations were determined using HPLC-MS (series 1100; Hewlett-Packard, Wilmington, DE). Samples were mixed with 2 ml n-butylchloride, shaken for 60 min, centrifuged (1,500*g*, 10 min), and frozen using dry ice for 15 min. After evaporation to dryness (continuous nitrogen flow, 45°C), the extraction residues were dissolved in 100 μl acetonitrile–water (73/27), and 50-μl aliquots were injected into the column. Chromatographic separation was achieved on an RP select B, Lichrospher 60, 250 × 3.5-μm column (Merck, Darmstadt, Germany) and C18 guard cartridge, using as mobile phase a 0.1% formic acid in a water-soluble acetonitrile–water gradient (820 μl/l, 73/27 v/v, 0.7 ml/min). The column oven temperature was 40°C. Detection of sufentanil was performed using mass spectrometry (MS-ESI, SIM). Standard curves were prepared by spiking sheep plasma with sufentanil (MW 387.2) at concentrations ranging from 0.0 to 7 ng/ml and with fentanyl (MW 337.2) as an internal standard at a concentration of 10 ng/ml. As an intraassay control, sheep plasma, spiked with 0.2 pg/ml sufentanil, was included with each batch of study samples.

Statistical Analysis

Changes over the time and between groups were analyzed by one- or two-way analysis of variance for repeated measurements, as appropriate, followed by Dunnett or Tukey test, respectively. If data were not normally distributed, Friedman repeated-measures analysis of variance on ranks was performed. A *P* value less than 0.05 was considered to be significant. Plasma con-

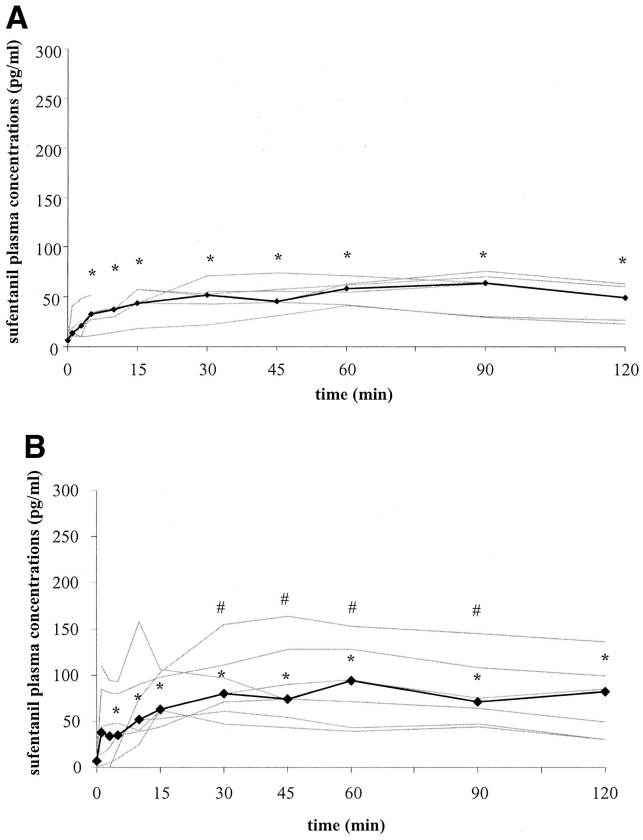

Fig. 1. (*Top*) Changes in maternal sufentanil plasma concentrations (pg/ml) after 25 μg intraamniotic sufentanil over time; n = 7; *superimposed thick line* = median; **P* < 0.05 *versus* 0 min. (*Bottom*) Changes of maternal sufentanil plasma concentrations (pg/ml) after 50 μg intraamniotic sufentanil over time; n = 7; *superimposed thick line* = median; **P* < 0.05 *versus* 0 min; #*P* < 0.05 *versus* fetus 50 μg intraamniotically.

centrations are presented as median (95% confidence interval); all other data are presented as mean ± SEM.

Results

A total of 12 animals were operated on. One ewe aspirated during emergence from anesthesia and was euthanized the next day; one fetus died 12 h after the procedure for unknown reasons. Eighteen treatments were performed in the remaining 10 sheep. In one case, the fetal arterial line clotted; therefore, only one treatment could be performed in this animal. One ewe had diarrhea and was excluded from one experiment. Moderate bleeding in one case from a uterine cotyledon during the operation did not interfere with experiments. Four samples were lost because of breakdown of the freezer. Successful plasma sample analysis was performed in seven cases in the 25-μg group and in seven cases in the 50-μg group.

Effects of Intraamniotic Sufentanil on Maternal Plasma Concentrations and Hemodynamics

After 25 μg intraamniotic sufentanil, maternal sufentanil plasma concentrations stabilized after 15 min at 44 (33–55) pg/ml (fig. 1, *top*). Fifty micrograms sufentanil intraamniotically tended to induce greater maternal blood concentrations (94 [65–123] pg/ml) compared with 25 μg sufentanil, but these were not significantly different. The initial increase took place in the same time frame (within 15 min; fig. 1, *bottom*). The highest concentration measured after 25 μg intraamniotic sufentanil was 76 pg/ml after 90 min. This same ewe achieved the highest plasma concentrations after 50 μg sufentanil intraamniotically (163 pg/ml after 45 min).

Neither 25 nor 50 μg intraamniotic sufentanil induced significant changes in maternal arterial pressure or heart rate (tables 1 and 2). Uterine blood flow, as an indicator of fetal supply, did not change significantly (fig. 2). Arterial blood gases and acid–base status remained unchanged in both groups, indicating that maternal respiratory depression did not occur (tables 1 and 2).

Effects of Intraamniotic Sufentanil on Fetal Plasma Concentrations and Hemodynamics

After 25 μg intraamniotic sufentanil, fetal plasma concentrations were achieved within the first 10 min (144 [73–215] pg/ml; fig. 3, *top*). Fetal heart rate tended to

Table 1. Maternal Hemodynamics and Arterial Blood Gases after 25 μg Intraamniotic Sufentanil

Time (min)	MMAP (mmHg) ± SEM	MHR (min^{-1}) ± SEM	pH ± SEM	P_{CO_2} (mmHg) ± SEM	P_{O_2} (mmHg) ± SEM
0	104 ± 3	125 ± 6	7.44 ± 0.0	26.5 ± 1.5	122.6 ± 7.3
1	102 ± 3	128 ± 6			
3	104 ± 3	128 ± 7			
5	104 ± 3	129 ± 5	7.43 ± 0.0	25.0 ± 1.4	125.3 ± 5.8
10	106 ± 4	127 ± 6			
15	103 ± 3	128 ± 6	7.43 ± 0.0	23.9 ± 1.3	127.1 ± 6.0
30	101 ± 3	127 ± 5	7.45 ± 0.0	25.1 ± 1.8	126.4 ± 6.0
45	104 ± 3	128 ± 6			
60	105 ± 3	128 ± 5	7.45 ± 0.0	25.0 ± 1.2	124.8 ± 4.8
90	108 ± 2	124 ± 4	7.44 ± 0.0	24.7 ± 1.6	126.9 ± 6.0
120	108 ± 2	125 ± 6	7.45 ± 0.0	24.7 ± 1.4	127.6 ± 4.2

Maternal mean arterial blood pressure (MMAP; mmHg), maternal heart rate (MHR; min^{-1}), maternal arterial pH, P_{CO_2}; mmHg), and P_{O_2}; mmHg) after 25 μg intraamniotic sufentanil. Data are presented as mean ± SEM; not significant.

Table 2. Maternal Hemodynamics and Arterial Blood Gases after 50 μg Intraamniotic Sufentanil

Time (min)	MMAP (mmHg) ± SEM	MHR (min^{-1}) ± SEM	pH ± SEM	P_{CO_2} (mmHg) ± SEM	P_{O_2} (mmHg) ± SEM
0	100 ± 4	120 ± 4	7.44 ± 0.0	28.5 ± 2.0	122.7 ± 4.5
1	103 ± 4	128 ± 4			
3	102 ± 5	119 ± 3			
5	101 ± 4	119 ± 3	7.43 ± 0.0	29.1 ± 2.0	119.1 ± 5.6
10	101 ± 5	120 ± 5			
15	104 ± 5	123 ± 3	7.43 ± 0.0	27.0 ± 2.1	123.1 ± 3.7
30	100 ± 5	122 ± 3	7.45 ± 0.0	27.8 ± 2.2	120.9 ± 4.2
45	97 ± 3	123 ± 4			
60	98 ± 5	119 ± 7	7.45 ± 0.0	25.8 ± 2.4	129.4 ± 6.7
90	103 ± 4	119 ± 4	7.44 ± 0.0	27.5 ± 2.2	122.1 ± 5.1
120	100 ± 4	117 ± 6	7.45 ± 0.0	27.7 ± 2.0	130.3 ± 7.3

Maternal mean arterial blood pressure (MMAP; mmHg), maternal heart rate (MHR; min^{-1}), maternal arterial pH, P_{CO_2}; mmHg), and P_{O_2}; mmHg) after 50 μg intraamniotic sufentanil. Data are presented as mean ± SEM; not significant.

increase from 162 ± 5 to 179 ± 7 min^{-1} (+10%) after 5 min and subsequently declined (120 min: 169 ± 7 min^{-1}). Fetal blood pressure was not affected (table 3). Sufentanil plasma concentrations did not peak earlier after 50 μg intraamniotic sufentanil compared with 25 μg and did not achieve significant higher plateau levels (maximum 175 [113–237] pg/ml at 60 min). Fetal heart rate increased from 154 ± 5 to 179 ± 7 min^{-1} (+16%) after 10 min and declined gradually to 161 ± 8 min^{-1} by the end of the study period. Again, arterial pressure did not change significantly (table 4). One fetus (belonging to the ewe with maximal plasma concentrations) reached maximal concentrations of 566 pg/ml 60 min after receiving 25 μg sufentanil intraamniotically. When receiving 50 μg intraamniotic sufentanil, the same fetus achieved maximal plasma concentrations of 508 pg/ml after 30 min (fig. 3, *bottom*).

pH, P_{CO_2}, and P_{O_2} did not change significantly in either group (tables 3 and 4).

Discussion

Our study demonstrates that administration of sufentanil intraamniotically induces plasma concentrations in the fetal lamb comparable to therapeutic concentrations in humans, which last for at least 120 min; plasma concentrations in the ewe were significantly less. No adverse hemodynamic maternal affects were observed.

Noxious stimuli to the fetus induce a rise in cortisol and β-endorphin levels and induce vigorous movements and breathing efforts.[23] Final thalamocortical connections, the anatomical correlate of pain perception, form at the 26th week of gestation.[15] Even earlier, nociceptive experience may be transmitted *via* transient thalamocortical fibers.[24] Indeed, because descending inhibitory

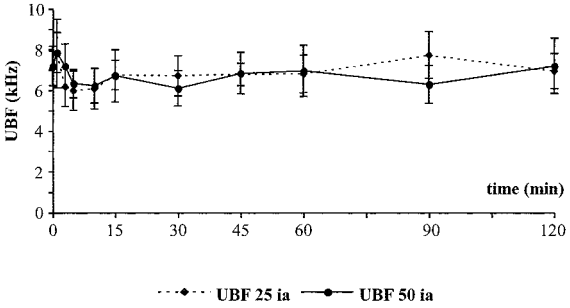

Fig. 2. Effects of 25 or 50 μg intraamniotic sufentanil on uterine blood flow (kHz); n = 10; mean ± SEM; not significant.

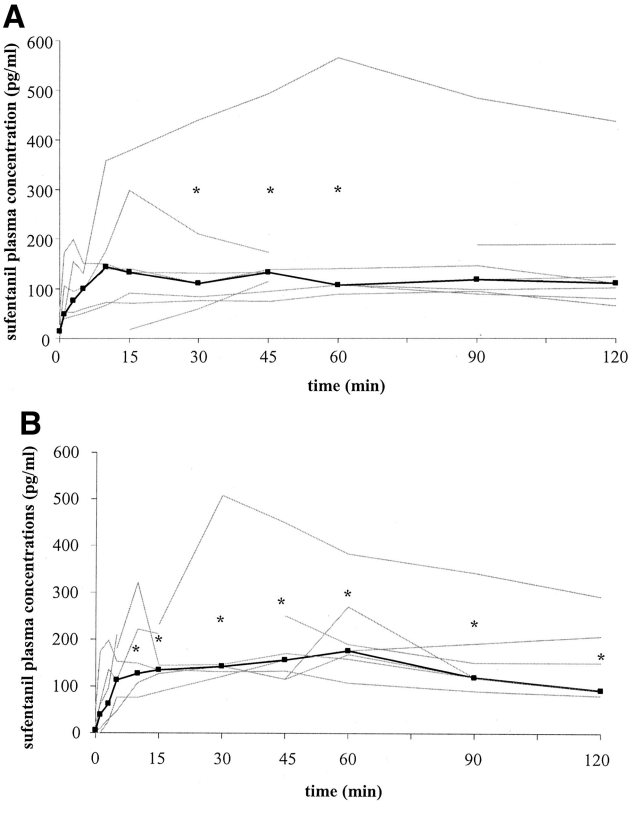

Fig. 3. (*Top*) Changes of fetal sufentanil plasma concentrations (pg/ml) after 25 μg intraamniotic sufentanil over time; n = 7; *superimposed thick line* = median; **P* < 0.05 *versus* 0 min. (*Bottom*) Changes of fetal sufentanil plasma concentrations (pg/ml) after 50 μg intraamniotic sufentanil over time; n = 7; *superimposed thick line* = median; **P* < 0.05 *versus* 0 min.

Table 3. Fetal Hemodynamics and Arterial Blood Gases after 25 μg Intraamniotic Sufentanil

Time (min)	FMAP (mmHg) ± SEM	FHR (min^{-1}) ± SEM	pH ± SEM	P_{CO_2} (mmHg)± SEM	P_{O_2} (mmHg) ± SEM
0	52 ± 3	162 ± 5	7.34 ± 0.0	38.2 ± 2.4	18.9 ± 1.7
1	53 ± 1	163 ± 6			
3	52 ± 2	173 ± 7			
5	52 ± 3	179 ± 7	7.36 ± 0.0	35.5 ± 1.6	20.5 ± 2.5
10	54 ± 3	176 ± 6			
15	52 ± 3	176 ± 8	7.35 ± 0.0	34.4 ± 2.7	19.6 ± 2.8
30	54 ± 3	162 ± 7	7.35 ± 0.0	37.1 ± 2.3	16.5 ± 1.6
45	56 ± 2	181 ± 6			
60	54 ± 2	174 ± 7	7.34 ± 0.0	37.6 ± 2.1	16.6 ± 1.1
90	53 ± 3	171 ± 6	7.34 ± 0.0	36.8 ± 2.4	16.8 ± 1.3
120	53 ± 3	168 ± 7	7.34 ± 0.0	39.3 ± 2.0	17.4 ± 1.2

Fetal mean arterial blood pressure (FMAP; mmHg), fetal heart rate (FHR; min^{-1}), fetal arterial pH, P_{CO_2}; mmHg), and P_{O_2}; mmHg) after 25 μg intraamniotic sufentanil. Data are presented as mean ± SEM; not significant.

pathways are not formed until birth, the fetus might be even more sensitive to painful stimuli. Human fetuses elaborate pituitary–adrenal, sympathoadrenal, and circulatory stress responses to physical insults as early as 18–20 gestational weeks.[23,25–27] Even if noxious stimuli are not consciously perceived, they can nevertheless influence sensory development.[28] Acute stress in fetuses or neonates can lead to permanent behavioral changes.[29–32] Circumcisions performed in nonanesthetized neonates increased the pain response to injections 6 months later.[33] Thus, fetal analgesia should be considered for all invasive procedures. However, because fetal surgical interventions range greatly in invasiveness (from minimally invasive procedures, such as blood sampling and *in utero* transfusions, to fetoscopic procedures and invasive open fetal surgery requiring hysterotomy[34]), the degree of postoperative fetal analgesia required depends on the procedure performed.

The chronically instrumented pregnant sheep preparation is an established model to study placental transfer.[35] It permits serial fetal and maternal blood sampling and continuous recording of vital signs in an awake, unrestrained animal. Fetal size and development are comparable with that in humans. Nevertheless, extrapolation from animal data to humans should always be done with caution. Sheep have an epitheliochorial placenta, which is less permeable to hydrophilic compounds than the hemochorial placentas of primates and rodents. However, this difference should have a minor influence on the transfer of lipid-soluble compounds.

Previous investigations in animals and humans have demonstrated that several intraamniotically administered compounds readily gain access to the fetus. Gilbert *et al.*[17] injected 1–25 μg arginine vasopressin intraamniotically in pregnant sheep (128 days' gestation) and measured significant increases in vasopressin concentrations in fetal plasma and urine, as well as increases in fetal arterial and venous pressures and decreases in urine flow and heart rate. Intraamniotic administration of digoxin in pregnant sheep induced fetal plasma concentrations approximately 10 times greater than measured maternal concentrations.[16] Cortisol is detectable in sheep fetal blood 30 min after intraamniotic administration.[36] Intraamniotic thyroxine has been used to prevent infant respiratory distress syndrome in toxemic human pregnancies.[19] Our findings extend these previous reports to a novel drug class.

Table 4. Fetal Hemodynamics and Arterial Blood Gases after 50 μg Intraamniotic Sufentanil

Time (min)	FMAP (mmHg) ± SEM	FHR (min^{-1}) ± SEM	pH ± SEM	P_{CO_2} (mmHg)± SEM	P_{O_2} (mmHg) ± SEM
0	50 ± 2	154 ± 5	7.36 ± 0.0	42.1 ± 3.1	18.2 ± 1.2
1	53 ± 2	165 ± 5			
3	51 ± 3	170 ± 6			
5	50 ± 4	170 ± 4	7.36 ± 0.0	39.0 ± 4.1	15.8 ± 4.5
10	54 ± 3	179 ± 8*			
15	51 ± 4	175 ± 7*	7.37 ± 0.0	38.9 ± 3.2	18.9 ± 1.9
30	54 ± 3	178 ± 8*	7.37 ± 0.0	36.1 ± 3.4	18.4 ± 1.3
45	50 ± 4	169 ± 5			
60	50 ± 3	167 ± 7	7.36 ± 0.0	38.7 ± 3.4	18.1 ± 0.5
90	51 ± 3	160 ± 6	7.37 ± 0.0	38.6 ± 2.8	18.7 ± 1.2
120	50 ± 3	161 ± 8	7.37 ± 0.0	38.8 ± 3.0	18.5 ± 0.9

Fetal mean arterial blood pressure (FMAP; mmHg), fetal heart rate (FHR; min^{-1}), fetal arterial pH, P_{CO_2}; mmHg), and P_{O_2}; mmHg) after 50 μg intraamniotic sufentanil. Data are presented as mean ± SEM.

* $P < 0.05$ *versus* 0 min.

The sustained fetal sufentanil plasma concentrations observed can have multiple reasons. During fetal development, blood flowing from the placenta partially bypasses the liver (through the ductus venosus arantius); in addition, fetal hepatic biotransformation pathways are immature. Whereas the distribution half-life of sufentanil does not seem to be age related (164 ± 69 min in adults[37]; 187 ± 31 min in neonates, infants, children, and adolescents[38]), the elimination half-life of sufentanil is increased threefold in neonates compared with the older population.[38]

Concentrations of α_1-acid-glycoprotein in fetal plasma are 5–10 times lower than in adults. Near term, the fetal/maternal serum concentration ratio reaches 0.37.[39] Therefore, a greater amount of the unbound (active) fraction is available in fetal plasma.[40] This should be taken into account when interpreting our data, as we measured total serum sufentanil concentrations only and did not separate between bound and unbound fractions. Finally, our results might modestly underestimate the actual sufentanil plasma concentrations as samples were analyzed off-line and the sufentanil concentration decreases with storage time.[41]

The appropriate dosing for intraamniotic opiates is not known. Sheep are less sensitive to opioids than humans. Thus, the lack of observed hemodynamic responses to opioids in this study does not exclude hemodynamic side effects in humans, and we did not study antinociceptive effects of sufentanil in this model. Analgesic sufentanil concentrations in human fetuses have not been determined. In adults, minimal effective sufentanil concentrations in postoperative pain management ranged between 10 and 560 pg/ml, but a minimal concentration of 30 pg/ml seems to be necessary for a consistent response.[42] In pediatric cardiovascular patients, plasma concentrations of sufentanil were determined at the time when additional anesthetic supplementation (after induction with 10–15 μg/kg sufentanil) was required to suppress hemodynamic responses to surgical stimulation. The measured concentration was 2.51 ng/ml in neonates, significantly higher than the concentrations of 1.58, 1.53, and 1.56 ng/ml observed in infants, children, and adolescents, respectively.[38] However, all patients had cardiovascular diseases, which could have affected the dosages; the neonates did not receive premedication (but older patients did); and these concentrations were needed to suppress a surgical stimulus and do not represent postoperative needs. Corresponding fetal sufentanil plasma concentrations have not been evaluated so far.

Although fetal hemoglobin concentrations tended to decrease in both intraamniotic groups (as a sign of hemodilution), these changes were not significant. Fetal heart rate increased modestly after 50 μg sufentanil administration. However, because the study did not include a saline control group (which would have entailed more fetal blood sampling and possibly would have resulted in hemodynamic effects), we cannot determine whether the cause of this effect was the opioid or the intraamniotic injection.

In conclusion, we showed that the fetal lamb absorbs intraamniotic sufentanil and achieves significantly greater plasma concentrations than the ewe. Neither 25 nor 50 μg intraamniotic sufentanil adversely affected fetal or maternal hemodynamics. This suggests that intraamniotic administration of drugs may be a potential approach to provide postoperative anesthesia after fetal surgery.

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