

Fetal and Maternal Plasma Concentrations After Intraamniotic Fentanyl Administration in Instrumented Pregnant Sheep

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Introduction: Fetal anesthesia and analgesia appear necessary during fetal surgical intervention, as noxious stimuli can generate a physiochemical fetal stress response *in utero* as early as 16 weeks gestation. While such a response may have long-term implications for fetal development, it can also result in preterm labor and, ultimately, the delivery of a nonviable fetus. Most fetal interventions today are performed under maternal general anesthesia, thus providing some fetal anesthesia via placental transfer of inhaled agents. As general anesthesia may increase the anesthetic-related risks to the pregnant patient, alternative methods of fetal drug delivery are warranted. Intraamniotically administered fentanyl may be a feasible option to deliver intraoperative and postoperative selective fetal analgesia if it produces therapeutic plasma concentrations in the fetus without significant levels in the mother.

The primary goals of this study were: (1) to examine and maternal response to, and pharmacokinetics of, intraamniotic fentanyl delivery in an instrumented pregnant sheep model; (2) to determine both fetal and maternal serum fentanyl levels after *in vivo* intramniotic administration of fentanyl at three different dosages.

Methods: After approval from both IACUC and the Animal Resources at Children's Hospital Boston, Harvard Medical School, fifteen time-bred pregnant ewes with a mean gestational age of 122 days (term 145 days) were studied. Fetal lambs were divided into three groups of five. All groups received the same induction and general anesthetic maintenance, hemodynamic monitoring, uterine access, and vascular access as described elsewhere.¹ Group 1 received 10ug/kg (estimated fetal weight) of intraamniotic fentanyl, Group 2 received 25 ug/kg, and Group 3 received 100 ug/kg of fentanyl. All groups had fetal and maternal blood samples drawn at time 0 and 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, and 240 minutes after administration. Fentanyl concentration was measured by a standard quantitative sandwich enzyme immunoassay technique, described elsewhere.²

Statistical Analysis: A two-way repeated-measures analysis of variance (ANOVA) was applied to estimate mean plasma fentanyl levels and 95% confidence intervals with dose and mother-fetus treated as factors, time as a varying covariate, and the mother-fetus pairs defined as the subject variable in the mixed model. Statistical significance was set up as a two-tailed value of $P < 0.05$.

Results: Fetal plasma fentanyl levels were significantly higher than maternal levels at each time point except 0 for the 100 $\mu\text{g}/\text{kg}$ dose (all $P < 0.001$) while no difference were detected at any time point from 0 to 240 minutes between mothers and fetuses for the 10 $\mu\text{g}/\text{kg}$ or 25 $\mu\text{g}/\text{kg}$ doses (all $P > 0.05$) (Figure 2). For example, at the 100 $\mu\text{g}/\text{kg}$ dose, the mean plasma fentanyl level at 60 minutes was 0.3 ng/ml for mothers (95% confidence interval, 0 – 0.6 ng/ml) and 3.2 ng/ml (95% CI, 2.9 – 3.5 ng/ml) for fetuses ($P < 0.001$). However, no significant mean differences were observed between maternal and fetal fentanyl levels at 60 minutes for the 10 $\mu\text{g}/\text{kg}$ dose (0.02 ng/ml, 95% CI, 0 – 0.31 vs. 0.2, 95% CI, 0 – 0.44 ng/ml, respectively; $P = 0.58$) or the 25 $\mu\text{g}/\text{kg}$ dose (0.04 ng/ml, 95% CI, 0 – 0.33 vs. 0.6 ng/ml, 95% CI, 0.26 – 0.84 ng/ml; $P = 0.11$) [see Figure 1]. Maternal mean arterial pressure, heart rate, pH, pCO₂, and pO₂ as well as fetal pH measurements demonstrated no significant differences over the duration of the procedures in all groups [see Table 1 for data from highest dose group].

Figures and Table for: **Fetal Plasma Concentrations after Intraamniotic Fentanyl Administration in Instrumented Pregnant Sheep**

Figure 1: Maternal versus fetal fentanyl concentrations after intraamniotic delivery of fentanyl. (* represents $p < 0.05$ for fetal plasma concentration of fentanyl versus maternal concentration at same time and dose range.)

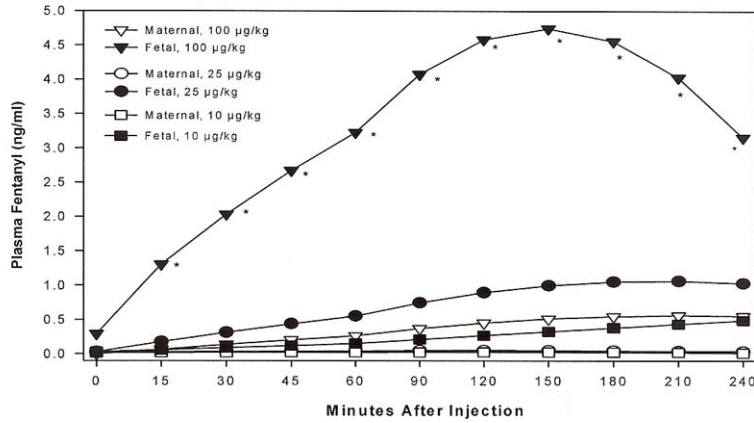


Table 1: Maternal Hemodynamics and Maternal and Fetal Arterial Blood Gases after 100 ug/kg Estimated Fetal Weight Intraamniotic Fentanyl

Time	HR (bpm)	SEM	MAP (mmHg)	SEM	Maternal pH	SEM	Maternal pCO2	SEM	Maternal pO2	SEM	Fetal pH	SEM
0	120	5	95	5	7.54	0.05	36.40	6.68	388.00	43.70	7.23	0.06
5	116	6	102	4	7.53	0.05	37.88	6.15	391.75	34.23	7.23	0.07
15	124	6	101	4	7.52	0.04	37.65	6.21	391.50	29.64	7.22	0.11
30	128	4	103	5	7.52	0.04	38.53	6.75	393.00	48.98	7.26	0.07
60	129	5	102	4	7.52	0.04	38.23	7.39	399.00	52.15	7.28	0.09
90	122	5	99	6	7.51	0.05	40.50	7.52	414.50	85.22	7.27	0.10
120	117	6	104	4	7.49	0.07	41.90	11.81	409.25	70.75	7.27	0.10
240	121	5	99	4	7.46	0.04	47.40	2.80	459.50	34.65	7.23	0.14

Maternal mean arterial blood pressure (MAP; mmHg), maternal heart rate (HR; bpm), maternal arterial pH, PCO2 (mmHg), and PO2 (mmHg) Data are presented as mean +/- SEM; not significant.

Conclusion: Our data analysis indicates that at a dose of 100 ug/kg (estimated fetal weight), fentanyl delivered into the amniotic fluid produces measurable concentrations in fetal plasma and that these concentrations are statistically different than those found in the paired mother at every time point measured except time 0. While there were trends toward measurable difference observed in the 25 ug/kg group, none met criteria for significance. In addition, there were no significant differences found between maternal and fetal plasma levels in the 10 ug/kg group. Although further investigation is planned, intraamniotic fentanyl administration is a promising new technique for direct fetal analgesia administration with minimal maternal exposure and hemodynamic perturbation.

References:

1. Vertommen JD, Marcus MA, Van Aken H: The effects of intravenous and epidural sufentanil in the chronic maternal-fetal sheep preparation. *Anesth Analg* 1995; 80:71-5
2. Burtis CA, Ashwood ER, Bruns DE: *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*, 4th edition. Philadelphia: Saunders, 2005.