OBSTETRIC ANESTHESIA AND PERINATOLOGY I

A827

TITLE: PREGNANCY ALTERS THE PHARMACODYNAMICS OF COCAINE IN RATS

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The purpose of this study was to test the hypothesis that pregnancy may influence the pharmacodynamics of cocaine.

Fifteen chronically catheterized term pregnant (P) and 18 nonpregnant (NP) female Sprague-Dawley rats were used. Cocaine (5mg/kg) was infused intravenously over a 15 min period to each adult animal. Arterial pressure and heart rate were monitored throughout. Cardiac output and organ blood flow were measured using the microsphere method, prior to and at the end of cocaine infusion. Additional blood samples were also withdrawn at the end of infusion for cocaine determinations. All animals were killed and several organs removed. Fetal blood was sampled by cardiac puncture, and brain, heart and liver were obtained. Cocaine concentrations in all blood and tissue samples were determined, using a gas chromatographic procedure. In a separate study, blood was obtained from 6 P and 6 NP rats for colorimetric measurement of plasma cholinesterase activity (1). ANOVA and t test were performed, where applicable, for statistical analyses. A p value of less than 0.05 was considered significant.

Cocaine infusion resulted in hypertension associated with a fall in cardiac output from 33.9±1.1 to 26.3±1.8 ml/min/100g in P, and from 31.6±1.3 to 27.2±1.4 ml/min/100g in NP rats. These changes were statistically significant in the P group. In general, cocaine infusion decreased regional blood flow; the decrease was statistically significant in the brain in both P and NP animals, while it was significant in the heart and placenta in the P group. A decrease in placental blood flow (from 1.42±0.16 to 0.72±0.17 ml/min/g) was striking. The mean plasma cocaine concentration in the P group was significantly lower, 1,656±126 vs. 2,184±202 ng/ml in the NP animals. Overall tissue concentrations were similar, while tissue to plasma concentration ratios were higher in the P group. Cocaine concentration in fetal plasma was 366±21 ng/ml, resulting in a fetal to maternal concentration ratio of 0.23±0.05. Drug concentrations in the fetal brain and heart were 11 and 8 times lower than corresponding maternal organs. Tissue to plasma concentration ratios in these fetal organs were also significantly lower than in the mother. Plasma cholinesterase activity in P (2,160±197 mU/ml) was significantly higher than in NP animals (1,4454±134 mU/ml).

These observations indicate that pregnancy enhances the hemodynamic effects of cocaine. The lower blood concentrations of the drug in P rats were probably due to the greater volume of distribution and higher plasma cholinesterase activity. The overall values for the tissue to plasma concentration ratios of cocaine in the P were higher than those in the NP group indicating that pregnancy increases tissue uptake of the drug. Low fetal plasma and tissue concentration of cocaine were probably related, in part, to a severe reduction in the placental blood flow induced by the drug.

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Reference
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Colorimetric determination of serum cholinesterase and its genetic variants by the propionyl-thiocholine-dithiobis [nitrobenzoic acid] procedure. Clin Chem 19:1309,1973

A828

Title: PLACENTAL TRANSFER OF LIDOCAINE DURING MATERNAL HYPOXIA

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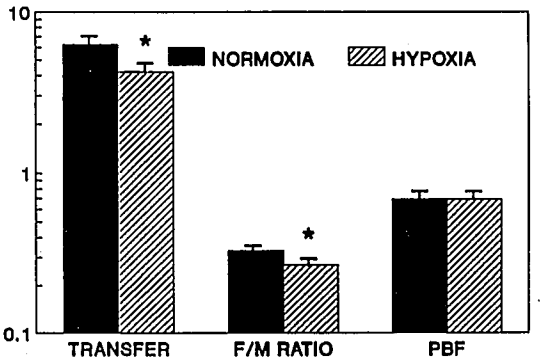
Introduction: Maternal hypoxia may suddenly develop as a complication of epidural anesthesia. We have studied how maternal hypoxia affects placental transfer of lidocaine (Lido) in the isolated human placental cotyledon.

Methods: Placentae were obtained from 8 healthy term pregnant women. The placental cotyledon and fetal umbilical vein (UV) and artery (UA) were cannulated and perfused with diluted plasma (1:3) containing 5 μg/ml of Lido. The maternal cotyledon was perfused at 900 ml/min; fetal UA at 300 ml/min. Measured were: lactate, glucose, albumin, Lido (radioimmunofluoroscent assay), pyruvate, pH, PCO_2, PO_2, globulin in maternal inflow and outflow and in the fetal UV outflow, fetal perfusion pressure (FPP) and UV outflow rate (UVFR). Fetal/maternal Lido ratio (F/M) was calculated. The net amount of Lido transferred to fetus was derived by multiplying UVFR by UV Lido concentration. Protein bound fraction (PBF) of Lido was done by centrifugation dialysis. The placenta was first perfused with normoxic perfusate (pH 7.36, PCO_2 38 mmHg, PO_2 196 mmHg) for 30 mins followed by hypoxic biophase (pH 7.38, PCO_2 36, PO_2 29) for 30 mins. Measurements were made at end of each period. Results were expressed as mean±1 SE and analyzed using t-test.

Results: UVFR and FPP decreased significantly respectively from 4.2±0.1 ml/min and 47±4 mmHg during normoxia to 3.4±0.3 ml/min and 38±5 mmHg during hypoxia ($p<0.01$). During hypoxia, F/M ratio and the net transfer of Lido decreased with no difference in PBF (Fig). No other measurements changed significantly during hypoxia.



Legend: *=significantly different from normoxia ($p<0.01$). PBF=protein bound fraction (UV). Transfer=total lidocaine (ug/min) entering the fetal circulation.

Discussion: Data show that during maternal hypoxia both F/M ratio and total fetal transfer of Lido decrease. Maternal hypoxia causes placental vasodilatation as evidenced by falling FPP. The diminished UVFR further suggests stagnant circulation within the placenta. Decreased transfer may be due to diminished passage of Lido across the placenta and/or retention within the placenta.