Title: HYDRALAZINE DOES NOT IMPROVE DECREASED UTERINE BLOOD FLOW DURING COCAINE-INDUCED HYPERTENSION IN THE PREGNANT EWE

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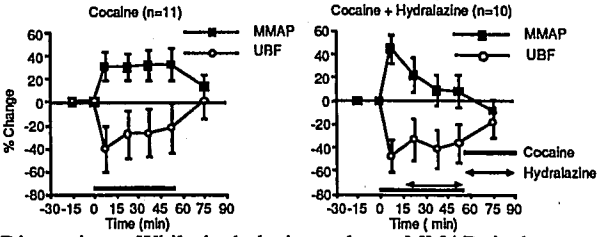
Introduction: Acute effects of cocaine in pregnant women include maternal hypertension, increase in placental abruption and increase in fetal distress leading to cesarean section. Studies in the pregnant ewe have shown that acute cocaine administration to the mother increases maternal mean arterial pressure (MMAP) and reduces uterine blood flow (UBF). (1,2) Limited data are available concerning the acute cardiovascular effects of cocaine and its interaction with therapeutic drugs during pregnancy. Hydralazine has been shown to increase UBF in the treatment of phenylephrine-induced hypertension in the pregnant ewe. (3) However, the maternal and fetal response to hydralazine during acute cocaine intoxication is unknown. In this study we evaluated the impact of hydralazine on maternal and fetal cardiovascular hemodynamics, and acid-base status during acute cocaine intoxication in the pregnant ewe.

Methods: We studied pregnant ewes at 120 days gestation. Using the chronic maternal-fetal sheep preparation (3) MMAP, UBF, maternal heart rate (MHR), fetal mean arterial pressure and fetal heart rate were recorded. Fetal and maternal arterial blood samples were obtained for cocaine levels and acid-base status. Intravenous cocaine was given for 55 min to the ewe to induce and maintain both increased MMAP and reduced UBF. The control group (n=11) received cocaine alone, while the study group (n=10) also received hydralazine, starting 15 min after the cocaine administration. Both drugs were discontinued 55 min after the start of the cocaine, followed by a 35 min recovery period. Statistical analyses were performed using repeated measures ANOVA and Dunnett t-testing. ($P < 0.05$).

Results: In the control group cocaine administration resulted in a 32% increase in MMAP and a 26% reduction in UBF. During the 35 min recovery period, UBF returned to base-line values. In sheep given cocaine and hydralazine, hydralazine increased MHR by 121% and restored MMAP toward base-line after 20 min of therapy, but UBF remained reduced even through the recovery period. Maternal plasma cocaine levels ranged from 111 to 3004 ng/ml, but were typically similar to those levels seen in cocaine intoxication. Similar levels were seen in the fetus. Fetal pH and O_2 saturation declined significantly in both groups.



Discussion: While hydralazine reduces MMAP, it does not improve UBF. Further, the dramatic rise in MHR is potentially life threatening. Although extrapolation of animal data to humans may not always be valid, it would appear that hydralazine is not the drug of choice in cocaine-induced maternal hypertension.

References: 1. Am J Obstet Gynecol 155: 883-888, 1986 2. JAMA 257: 957-961, 1987 3. Obstet Gynecol 50: 598-602, 1977.

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TITLE: AGE-RELATED COCAINE UPTAKE IN RATS

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Women who used cocaine during pregnany often give birth to infants showing severe neurologic and behavioral abnormalities. Since cocaine stimulates uterine activity, many babies are delivered shortly after an acute intrauterine drug exposure and have significant blood and tissue concentrations of cocaine. The current study was performed to compare the disposition of cocaine in newborn rats with that in adults.

Fifty-three newborn (NB) and 18 nonpregnant adult female (NP) Sprague-Dawley rats were used. All animals received an intraperitoneal injection of cocaine HCl, 10 mg/kg. They were killed at predetermined intervals from 5 to 240 min thereafter. Blood sample was withdrawn by cardiac puncture, and brain, heart, and liver, as well as the remainder of the body of NB, were obtained for determination of cocaine concentrations, using the GLC-NPD technique. ANOVA and Student's t-test were used for statistical analyses. A $p<0.05$ was considered significant.

None of the animals demonstrated any major signs of intoxication after cocaine administration. In both groups of rats, plasma and tissue concentrations reached their peak at 15 min; cocaine disappeared from NP faster than those from NB (Table).

Mean±SE cocaine concentrations in plasma (ng/ml), and tissues (μg/g) obtained at 15 and 60 min.

	Newborn		Adult	
Time	15 min	60 min	15 min	60 min
Plasma	1217±125	445±124	880±50*	119±6*
Brain	4.8±1.3	4.3±0.6	4.2±0.4	0.4±0.1*
Heart	7.2±1.2	3.4±0.6	3.2±0.1*	0.2±0.1*
Liver	20.7±4.0	4.6±1.1	2.9±0.4*	0.5±0.1*
Carcass	13.7±2.8	10.3±1.2		

*Significantly different from newborn.

We have observed that: 1) plasma and tissue cocaine concentrations tended to be higher in NB than in NP after ip injection; 2) after 15 min, plasma and tissue concentrations declined more slowly in NB than in NP. This was particularly significant in NB brain. We have demonstrated previously that once cocaine enters the circulation, its affinity for brain is similar in the fetus and the mother (1). These results suggest that the effects of cocaine may be greater in the newborn than in the adult.

Reference
1) American Society of Anesthesiologists Annual Meeting, 1989, A894.

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