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Hydralazine Does Not Restore Uterine Blood Flow during Cocaine-induced Hypertension in the Pregnant Ewe

Jan D. Vertommen, M.D., Samuel C. Hughes, M.D.,† Mark A. Rosen, M.D.,‡ Sol M. Shnider, M.D.,§ Mauricio I. Espinoza, M.D.,¶ Cheryl P. Messer, M.D.,* Judy L. Johnson,** Julian T. Parer, M.D.††*

Cocaine abuse is widespread, and its use by the parturient has potential significant adverse effects in both the mother and the newborn. This study was undertaken in gravid ewes to determine the effects of treatment of cocaine-induced hypertension with hydralazine (Apresoline®) on the maternal and fetal cardiovascular systems, catecholamine response, blood gas and acid–base status, and uterine blood flow (UBF). Twenty-one experiments were performed in 15 chronically instrumented ewes near term gestation. After a 30-min control period, cocaine was given intravenously to all ewes for 55 min to induce and maintain increased maternal mean arterial pressure (MMAP) and reduced UBF. The sheep were randomly assigned to receive either cocaine alone (n = 11, control group) or hydralazine (n = 10, treatment group), starting 15 min after the cocaine administration. Both drugs were discontinued 55 min after the start of the cocaine administration, followed by a 35-min recovery period. In the control group, cocaine administration resulted in a 31 ± 13% (SD) increase in MMAP ($P < 0.05$) and a 26 ± 21% reduction in UBF ($P < 0.05$). In the treatment group, the initial cocaine administration resulted in a similar increase in MMAP and decrease in UBF. Hydralazine therapy restored MMAP toward baseline after 20 min of administration, but UBF remained reduced (37 ± 17%) throughout therapy ($P < 0.05$) and recovery (18 ± 13%) ($P < 0.05$). The maternal heart rate increased maximally by 121 ± 33% ($P < 0.05$) after the administration of hydralazine, compared with a 14 ± 21% increase ($P < 0.05$) in the control group. The maternal plasma epinephrine concentration increased significantly in both groups, as did fetal norepinephrine, which remained increased 35 min after discontinuation of the cocaine and hydralazine. Fetal *p*H and oxygen hemoglobin saturation decreased significantly in both groups after cocaine administration and remained significantly reduced throughout the recovery period. Thus, in the near-term pregnant ewe, treatment with hydralazine ameliorated a cocaine-induced hypertension, but brought about a profound maternal tachycardia and failed to restore a cocaine-induced reduction in UBF. We conclude that hydralazine may not be the drug of choice to treat cocaine-induced hypertension in the gravid ewe; these findings may have significance for the parturient as well. (Key words: Anesthesia, obstetric: maternal hypertension; uterine blood flow. Anesthetics, local: cocaine. Fetus: drug effects. Sympathetic nervous system, catecholamines: dopamine; epinephrine; norepinephrine.)

* Research Fellow, Obstetrical Anesthesia.

† Associate Professor of Clinical Anesthesia.

‡ Associate Professor of Clinical Anesthesia, Obstetrics, Gynecology, and Reproductive Sciences.

§ Professor and Vice Chairman of Anesthesia; Professor of Obstetrics, Gynecology and Reproductive Sciences.

¶ Research Fellow in Obstetrics, Gynecology and Reproductive Sciences.

** Staff Research Associate.

†† Professor of Obstetrics, Gynecology and Reproductive Sciences; Associate Staff, Cardiovascular Research Institute.

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Address reprint requests to Dr. Hughes: San Francisco General Hospital, Department of Anesthesia, 3S-50, 1001 Potrero Avenue, San Francisco, California 94110.

THE LAST DECADE has seen a dramatic increase in the use of cocaine, especially "crack" cocaine (cocaine freebase), the alkaloid form that does not decompose when burned and thus is easily self-administered by smoking.[1,2] When burned, it vaporizes readily and has a high bioavailability. It is believed that 30 million people in the United States have used cocaine at least once and that 5 million are habitual users.[2–4] Regrettably, many of these people are parturients or women of reproductive age who may incur a wide range of possible deleterious effects to both self and fetus.[5–15]

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).[16,17,‡‡] A variety of vasoactive drugs are currently available for management of acute hypertension, but the optimal choice for the parturient with acute cocaine intoxication is unknown. The most common drug currently used appears to be hydralazine (Apresoline®), for which there is widespread clinical and investigative experience.[18] However, the effects of hydralazine on UBF in the pregnant patient with cocaine intoxication have not been studied. The purpose of the present investigation is to determine whether treatment of cocaine-induced hypertension with hydralazine is effective in stabilizing the maternal cardiovascular changes and restoring decreased UBF toward normal. In addition, we investigated the effects of cocaine and treatment of cocaine-induced hypertension with hydralazine on the maternal and fetal blood gases and acid–base status, and catecholamine response.

Materials and Methods

SURGICAL PREPARATION

The protocol was approved by the Committee on Animal Research, University of California, San Francisco.

‡‡ Foutz SE, Kotelko DM, Shnider SM, Thigpen JW, Rosen MA, Brookshire GL, Koike M, Levinson G, Elias-Baker B: Placental transfer and effects of cocaine on uterine blood flow and the fetus (abstract). ANESTHESIOLOGY 59:A442, 1983.

Studies were performed in 15 pregnant ewes of Western Dorsett breed with a mean gestational age of 127 ± 1 days (SD), range 125–131 days (term = 145 days). The animals were fasted for 24 h prior to surgery. After sedation with an intramuscular injection of ketamine 10 $mg \cdot kg^{-1}$, anesthesia was induced using halothane 2–3%. After the trachea was intubated, the animals' lungs were mechanically ventilated (Ventimeter Air Shields, Hartboro, PA), and anesthesia was maintained using halothane 1–1.5% in oxygen.

Using sterile surgical technique, we inserted polyvinyl catheters into the maternal superior vena cava *via* a jugular vein, into the aorta *via* both a carotid and a tibial artery, and into the inferior vena cava *via* a tibial vein. When all maternal catheters were inserted, we performed a midline laparotomy to expose the uterus and secure a precalibrated nonocclusive electromagnetic blood flow transducer, diameter 4–5.5 mm (C & C Instruments, Culver City, CA), around the uterine artery division, supplying the pregnant uterine horn. A hysterotomy was then carefully performed, the fetal hind limbs exteriorized, and the fetal inferior vena cava cannulated *via* a tibial vein and the aorta *via* two tibial arteries. Three electrocardiographic electrodes were sutured directly to the fetus, and a catheter was placed in the amniotic cavity to record amniotic fluid pressure. After replacement of the approximate volume of amniotic fluid lost during these procedures with sterile normal saline, the catheters and the leads of the electromagnetic flow probe and the electrocardiographic electrodes were tunneled subcutaneously and exteriorized through a small incision in the flank and then were placed in a cloth pocket.

After closure of the abdominal incision and recovery from anesthesia, the animals were allowed to stabilize for at least 48 h before the study began. During this period, the catheters were irrigated once daily with sterile heparinized saline and were filled with sterile heparin (1,000 μg/ml). The animals were allowed free access to water and a standard ovine diet and received penicillin G, kanamycin sulfate, and butorphanol.

Experimental Protocol

The animals were studied while either standing or sitting in a study cart which allowed access to food and water. During the study period, we measured the following variables continuously: MMAP and maternal heart rate, UBF, amniotic fluid pressure, fetal mean arterial pressure and fetal heart rate. The maternal and fetal arterial pressure were measured *via* the tibial artery catheters using a strain gauge (Statham P23Db, Hato Rey, Puerto Rico). Fetal arterial pressure was corrected by subtracting amniotic fluid pressure from fetal arterial pressure. UBF was measured using a flowmeter (Gould-Statham, SP 2202, Oxnard, CA). All variables were recorded using a polygraph recorder (Grass, Quincy, MA). The fetal heart rate also was recorded on a cardiotocograph (Hewlett-Packard model 8030A, Palo Alto, CA).

The maternal and fetal blood samples were drawn from the carotid and tibial catheters, respectively. All blood samples for blood gases and acid–base status were measured immediately after sampling (Corning, 158pH/blood gas analyzer, Medfield, MA) and corrected to maternal temperature (39° C). The hemoglobin oxygen saturation (Sa_{O_2}) of arterial blood from both mother and fetus also was measured (Radiometer, OSM^2 hemoximeter, Copenhagen, Denmark). Maternal and fetal blood samples were collected to measure plasma epinephrine, norepinephrine, and dopamine concentrations as well as serum cocaine and benzoylecgonine levels. Catecholamine and cocaine levels were assayed using previously described methods.[18,19] Interrun coefficients of variation were 1.01% for cocaine and 4.18% for benzoylecgonine. As little as 2 ng/ml cocaine and 5 ng/ml benzoylecgonine can be detected, but the assay is more accurate at concentrations of 10 ng/ml or more. With regard to the catecholamine assay, the intra- and interassay coefficients of variation for norepinephrine, epinephrine, and dopamine were 1.4, 2.7, and 2.0% and 5.5, 7.8, and 14.0%, respectively and were sensitive to at least 50 pg/ml.

After a 30-min control period during which baseline values of all variables were established, we administered a bolus of cocaine intravenously to all ewes *via* jugular vein to induce and maintain both increased MMAP and reduced UBF. The cocaine was prepared at the hospital pharmacy and contained 20 mg/ml. Each animal received an initial bolus of 3 $mg \cdot kg^{-1}$ over a 60-s interval. Subsequent doses varied between 1.5 and 3 $mg \cdot kg^{-1}$ to achieve the adequate dose to maintain the reduction of UBF by approximately 25–30% and were given over a 30-s interval at 5, 10, and 15 min after the initial bolus. The dose administered at 15 min was then repeated as a fixed dose every 5 min, with the last dose being given at 55 min after the first. Eleven of 21 animals received only cocaine (control group), and the remaining 10 received intravenous hydralazine therapy in addition to cocaine (treatment group). Hydralazine therapy was started 1 min after the 15-min cocaine bolus and was given as 100-mg injections every 2–3 min to return MMAP to baseline values. At 55 min, hydralazine administration was discontinued simultaneously with cocaine. A recovery and observation period of 35 min followed.

Maternal and fetal arterial blood samples were taken before study and then at 30, 60, and 90 min after the start of the cocaine administration to permit blood gas analyses and measurement of plasma cocaine and catecholamine concentrations. After the protocol was completed, the fetus received a transfusion of blood withdrawn

from the ewe before the experiment to replace the blood that was lost from sampling.

The experiments were performed on consecutive days, and the order in which the experiments were performed was randomly assigned. Only one experiment was performed each day, and the animal was rested at least 24 h between experiments. In six animals, the maternal–fetal sheep preparation was stable and received the alternate protocol 1–3 days later.

Data were analyzed using repeated-measures analysis of variance, followed by Dunnett's *t* test to compare data with baseline values. Comparisons between groups were done by the unpaired Student's *t* test. A P value < 0.05 was considered significant. All values are expressed as the mean ± SD. Maternal and fetal heart rate and blood pressure and UBF are expressed as percent change.

Results

We performed a total of 21 experiments in 15 animals: 11 in the control group and 10 in the hydralazine group. There were no significant differences in maternal weight (54 ± 7 *vs.* 54 ± 6 kg), fetal weight (3186 ± 615 *vs.* 3111 ± 588 kg) or total dose of cocaine administered to the ewes in the two groups. The total dose of cocaine administered over the 55-min period was 26 ± 5 $mg \cdot kg^{-1}$ in the control group and 22 ± 4 $mg \cdot kg^{-1}$ in the hydralazine group ($P > 0.05$). There also was no difference between the two groups in baseline values of maternal and fetal blood gases or acid–base status (table 1).

The plasma cocaine concentrations achieved in the ewe and the fetus were similar in the two groups, and there were no significant differences at individual time periods between the cocaine (control) and hydralazine-treated group (fig. 1). Similarly, the measurements for benzoylecgonine, the chief metabolite of cocaine, were not significantly different between groups (fig. 2). The peak maternal cocaine concentrations occurred at 15 and 30 min and ranged from 2,454 ± 1,600 to 4,222 ± 3,628 ng/ml. In the fetus, the peak values at the same times ranged from 303 ± 138 to 462 ± 227 ng/ml. In the mother and fetus, only trace amounts of cocaine were measured at the 90-min sampling, 35 min after discontinuing cocaine administration.

In the control group, cocaine administration resulted in an initial 31 ± 13 increase in MMAP and a 41 ± 20% decrease in UBF (fig. 3A). After 15 min, the increase in MMAP and the decrease in UBF stabilized at 32 ± 13 and 26 ± 21%, respectively. Maternal heart rate (fig. 4), fetal heart rate, and fetal mean arterial pressure (figs. 5

TABLE 1. Maternal–Fetal Blood Gases and Acid–Base Status after Cocaine Alone and Cocaine and Hydralazine

Time	*p*H	P_{CO_2} (mmHg)	P_{O_2} (mmHg)	Base Excess ($mEq \cdot l^{-1}$)	O_2 Hemoglobin Saturation
Maternal					
Baseline					
C	7.50 ± 0.04	34.9 ± 4.2	99.7 ± 6.1	5.8 ± 3.1	96 ± 6
C + H	7.51 ± 0.02	35.5 ± 3.0	98.7 ± 6.9	6.9 ± 1.9	96 ± 3
30 min					
C	7.51 ± 0.03	34.4 ± 4.1	100.3 ± 8.8	6.0 ± 4.1	95 ± 6
C + H	7.53 ± 0.03	32.7 ± 4.5	98.0 ± 11.4	6.5 ± 2.9	95 ± 3*
60 min					
C	7.53 ± 0.06	33.7 ± 3.6	97.4 ± 3.9	7.0 ± 3.9	96 ± 6
C + H	7.51 ± 0.05	29.6 ± 4.0*	100.2 ± 9.4	3.5 ± 4.9*	95 ± 3*
90 min					
C	7.51 ± 0.03	36.5 ± 2.0	98.6 ± 4.3	7.1 ± 2.8	96 ± 6
C + H	7.53 ± 0.05	31.2 ± 3.1	101.1 ± 6.5	5.3 ± 3.4	95 ± 3*
Fetal					
Baseline					
C	7.36 ± 0.04	50.7 ± 5.3	20.2 ± 4.3	3.5 ± 2.9	44 ± 14
C + H	7.35 ± 0.05	48.7 ± 4.1	20.2 ± 3.5	1.7 ± 4.7	41 ± 9
30 min					
C	7.29 ± 0.07*	55.1 ± 5.8*	17.1 ± 3.3*	0.3 ± 4.2*	27 ± 11*
C + H	7.30 ± 0.05*	54.0 ± 5.6*	17.1 ± 3.4*	−0.2 ± 3.7	19 ± 10*
60 min					
C	7.27 ± 0.10*	55.4 ± 6.9*	16.7 ± 2.6*	−0.9 ± 5.9*	27 ± 9*
C + H	7.27 ± 0.09*	51.5 ± 9.0	16.7 ± 3.4*	−3.7 ± 4.8*	26 ± 10*
90 min					
C	7.26 ± 0.13*	53.4 ± 7.1	18.2 ± 4.1*	−2.1 ± 7.3*	32 ± 13
C + H	7.28 ± 0.07*	48.2 ± 4.3	18.2 ± 3.2*	−3.6 ± 4.6*	31 ± 11*

Data are expressed as the mean ± SD. The control group received cocaine alone (C), and the treatment group received cocaine followed by treatment with hydralazine (C + H).
* $P < 0.05$, compared with baseline values.

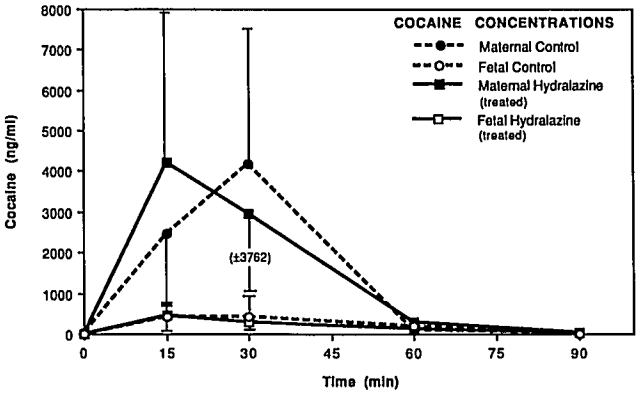

FIG. 1. Maternal (filled squares and circles) and fetal (open squares and circles) cocaine concentrations. The dotted lines represent the group that received cocaine only and the solid lines the group that received cocaine and treatment with hydralazine. The cocaine was begun at time 0 in both groups, and hydralazine was added at 16 min. Both drugs were discontinued at 55 min. Cocaine concentrations were measured at 15, 30, 60, and 90 min. Values are expressed in nanograms ± SD. The maternal control SD bar is on a broken scale at the 30-min point; all other SD bars are true to the vertical axis scale.

and 6) also increased significantly. After discontinuation of cocaine (at 55 min), UBF returned to baseline values while MMAP remained slightly increased (13 ± 11%) (fig. 3A). Fetal Sa_{O_2} and fetal pH decreased significantly from baseline values of 44 ± 14 to 27 ± 9% and 7.36 ± 0.04 to 7.27 ± 0.10, respectively, at the 60-min measurement point, 5 min after discontinuation of cocaine administration (55 min) (table 1). These fetal values remained de-

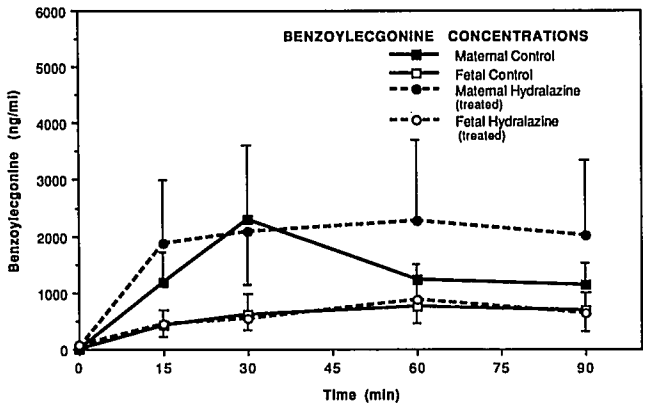

FIG. 2. Maternal (filled squares and circles) and fetal (open squares and circles) benzoylecgonine concentrations. The solid line represents the group that received cocaine only and the broken line the group that received cocaine and treatment with hydralazine. The cocaine was begun at time 0 in both groups, and hydralazine was added at 16 min. Both drugs were discontinued at 55 min. Benzoylecgonine concentrations were measured at 15, 30, 60, and 90 min. Values are expressed in nanograms ± SD.

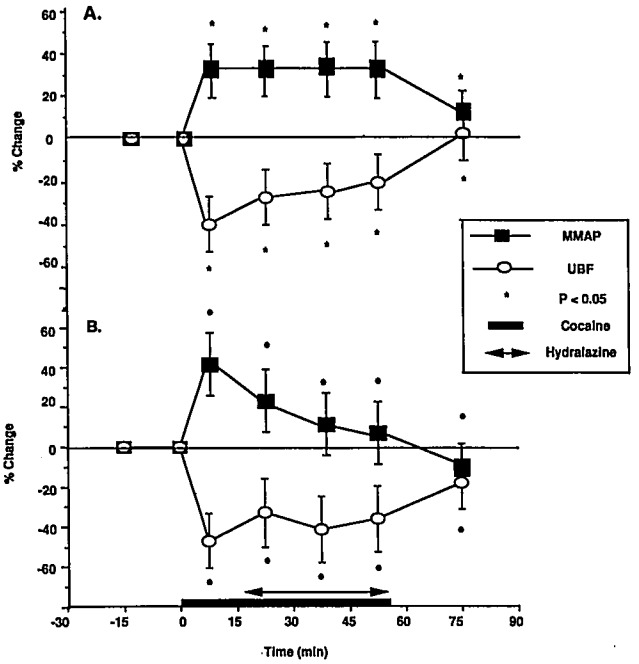

FIG. 3. Percent change in maternal mean arterial pressure (MMAP) and uterine blood flow (UBF) during cocaine administration (n = 11) (*A*). The heavy bar represents the time during which the cocaine was administered. *B:* Percent change in maternal mean arterial pressure (MMAP) and uterine blood flow (UBF) during cocaine administration and hydralazine therapy (n = 10). The arrow represents the time of hydralazine treatment. Both drugs were discontinued at 55 min. Values are expressed as ± SD. Changes are compared to baseline values with significance noted (*$P < 0.05$).

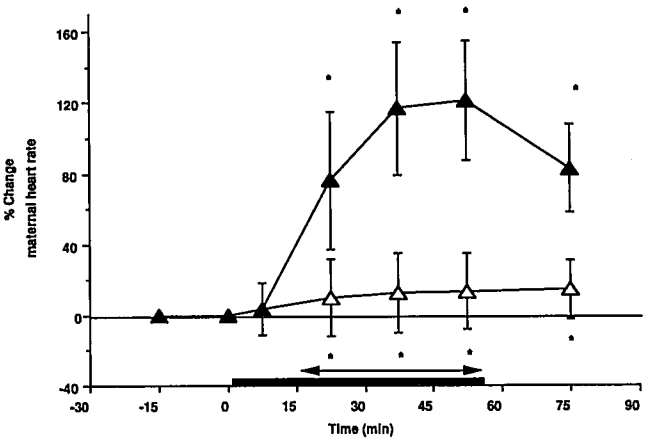

FIG. 4. Percent change in maternal heart rate during cocaine administration with hydralazine (n = 10) (filled triangles) and without (open triangles) hydralazine therapy (control, n = 11). Hydralazine treatment began at 16 min and was discontinued at 55 min and is represented by the arrow. The heavy bar represents the time of cocaine administration. Values are expressed as ± SD. Changes are compared to baseline values with significance noted (*$P < 0.05$).

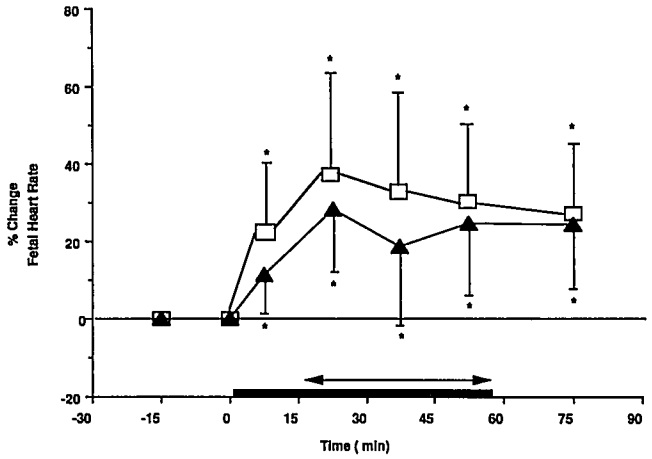

FIG. 5. Percent change in fetal heart rate during cocaine administration (control, n = 11) (open squares) and after treatment by hydralazine (n = 10) (closed triangles). The heavy bar represents the time during which the cocaine was administered, and the arrow represents the time of hydralazine administration in the treatment group. Values are expressed as ± SD. Changes are compared to baseline values with significance noted. (*$P < 0.05$).

creased at the end of the final observation period after cocaine had been discontinued for 35 min. There were no significant changes in the maternal blood gases or acid–base status in the group that received cocaine alone (table 1).

In the hydralazine group, the initial cocaine administration resulted in a 45 ± 13% increase in MMAP and a 47 ± 14% decrease in UBF (fig. 3B). Although hydralazine therapy tended to return MMAP to baseline values by 20 min, MMAP still remained increased by 13 ± 14% and UBF remained reduced by 37 ± 17% while hydralazine and cocaine were being administered. After discontinuation of both cocaine and hydralazine, MMAP decreased to 9 ± 10% below baseline values while UBF remained reduced by 18 ± 13%. As in the control group, fetal heart rate and fetal mean arterial pressure increased significantly with cocaine administration, and hydralazine had little effect on the fetal hemodynamic response (figs. 5 and 6). After initiation of the hydralazine therapy, maternal heart rate increased dramatically from 101 ± 11 to 221 ± 24 beats per min from baseline (121%) (fig. 4). Fetal Sa_{O_2} and fetal *p*H decreased significantly from baseline when cocaine (followed by hydralazine) was administered, from 41 ± 9 to 26 ± 10% and from 7.35 ± 0.05 to 7.27 ± 0.1, respectively, at 60 min when both cocaine and hydralazine had been discontinued (table 1). Maternal *p*H did not change significantly, but significant decreases in base excess (from 6.9 ± 1.9 to 3.5 ± 4.9 mEq/l) and in P_{CO_2} (from 35.5 ± 3.0 to 29.6 ± 4 mmHg) were observed during hydralazine therapy that were not noted with cocaine alone. The maternal Sa_{O_2} decreased from 96 ± 3 to 95 ± 3% ($P < 0.05$) with cocaine administration and did not return to baseline during the protocol.

The catecholamine analysis revealed a significant increase from baseline values in maternal epinephrine in both study groups (table 2). The fetal epinephrine concentrations were significantly increased at 15 and 30 min from baseline in the group that received cocaine alone but showed no significant change from baseline with hydralazine administration. The fetal norepinephrine concentrations were significantly increased at numerous points in both groups (table 2) and remained increased (from baseline) at the 90-min point in the group that received hydralazine. The maternal norepinephrine concentrations were not increased by cocaine alone but were significantly increased at 30 and 60 min after treatment with hydralazine. Neither the maternal nor the fetal dopamine concentrations were increased from baseline values at any time period in the group that received cocaine alone, and only a minor change was detected in the hydralazine-treated group.

Discussion

Cocaine is known to act systemically as a sympathomimetic drug.[21] It acts at nerve terminals to block the reuptake of the neurotransmitters norepinephrine and epinephrine, producing excess transmitters at postsynaptic receptor sites. This produces the potential of severe vasoconstriction, hypertension, and tachycardia, although a central nervous system stimulant action and other

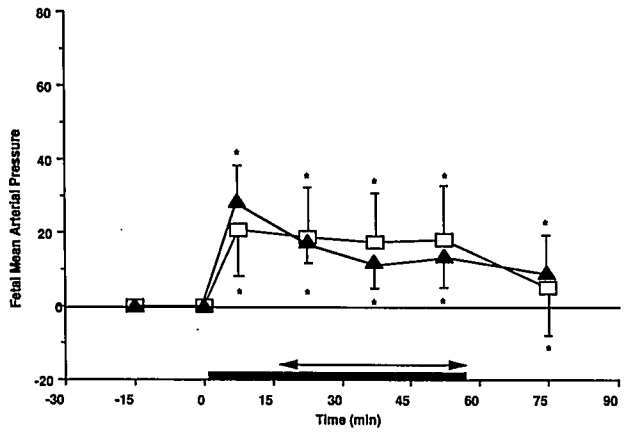

FIG. 6. Percent change in fetal mean arterial pressure during cocaine (n = 10) administration (control, n = 11) (open squares) and after treatment by hydralazine (n = 10) (closed triangles). The heavy bar represents the time during which the cocaine was administered, and the arrow represents the time of hydralazine administration in the treatment group. Values are expressed as ± SD. Changes are compared to baseline values with significance noted. (*$P < 0.05$).

TABLE 2. Maternal and Fetal Catecholamine Concentrations (picograms per milliliter)

	Epinephrine (Control) (n = 6)	Epinephrine (Hydralazine) (n = 9)	Dopamine (Control) (n = 5)	Dopamine (Hydralazine) (n = 10)	Norepinephrine (Control) (n = 7)	Norepinephrine (Hydralazine) (n = 10)
Maternal						
Baseline	38 ± 53	103 ± 157	483 ± 705	336 ± 649	753 ± 1219	748 ± 1256
15 min	208 ± 127*	259 ± 294	316 ± 268	240 ± 430	932 ± 482	932 ± 1092
30 min	202 ± 143*	414 ± 246*	459 ± 419	795 ± 1022	764 ± 699	2555 ± 1322*†
60 min	77 ± 50	296 ± 241*†	184 ± 175	1175 ± 977†	623 ± 501	3268 ± 1473*†
90 min	43 ± 55	119 ± 117	48 ± 50	325 ± 427	555 ± 683	1243 ± 703
Fetal						
Baseline	39 ± 50	343 ± 846	514 ± 970	1854 ± 4140	993 ± 762	1461 ± 1580
15 min	211 ± 98*	348 ± 533	864 ± 950	797 ± 1201	2733 ± 1431*	2880 ± 1564
30 min	220 ± 177*	327 ± 547	1266 ± 1475	773 ± 941	2463 ± 1283*	4773 ± 2918*
60 min	137 ± 106	1814 ± 4599	836 ± 1144	2034 ± 2975*	2924 ± 1700*	6005 ± 7464
90 min	69 ± 117	269 ± 536	861 ± 1241	1087 ± 1256	1544 ± 1411	2823 ± 999*†

All values are expressed as the mean ± SD.

* $P < 0.05$, baseline value compared to values at individual time periods.

† $P < 0.05$, control (cocaine only) *versus* hydralazine-treated group.

mechanisms may also be involved in cocaine's peripheral cardiovascular actions.[1] Placental vasoconstriction and reduced UBF observed with maternal cocaine administration in the ewe as seen in this study is significant, and repeated maternal (human) abuse of cocaine probably leads to fetal hypoxia and acidosis. Previous studies in our laboratory and others in pregnant ewes have shown that a single intravenous bolus of cocaine produces a transient dose-related increase in MMAP and a significant decrease in UBF.[16,17,‡‡] The chronic, repeated maternal use of cocaine may be more deleterious. On the other hand, the response may vary over time. However, the known acute effects in humans include maternal hypertension and tachycardia, so that intervention may be required for maternal or fetal indications.[15]

The choice of emergency treatment in a clinical situation would ideally be an agent that acts quickly in a controlled manner to reduce maternal blood pressure and counteract the uteroplacental vasoconstriction caused by cocaine without having adverse effects on mother or fetus. A number of drugs have been suggested or investigated as potential agents for the acute treatment of hypertension in the parturient, including labetalol,[22–25] esmolol,[26] nitroprusside,[27] nitroglycerin,[28] and hydralazine.[29] Most have been investigated for the treatment of preeclampsia, but not in cocaine-abusing parturients. We chose to study hydralazine because it appears to be the most commonly used drug to treat acute hypertension in the parturient and is used extensively by obstetricians at our institution. In addition, earlier investigation in the ewe suggested that hydralazine might be appropriate.[29]

Using the pregnant ewe model, Ring *et al.* demonstrated that when hypertension was induced by a continuous infusion of phenylephrine, an α agonist, and blood pressure was controlled by a titrated infusion of either nitroprusside or hydralazine, the hydralazine infusion tended to improve UBF, whereas nitroprusside did not.[29] This suggested that hydralazine might be helpful in treating the acute effects of cocaine. On the other hand, hydralazine causes direct relaxation of arterial vascular smooth muscle and has the disadvantage that it may induce reflex tachycardia. This would be particularly undesirable with the potential tachycardia of acute cocaine intoxication. Pregnancy increases the cardiovascular toxicity of cocaine in sheep, suggesting a possible increased risk for cardiac or vascular complications in the parturient using cocaine.[30]

After a single intravenous bolus of cocaine in sheep, MMAP and UBF quickly return to baseline values,[16,17,‡‡] making it difficult to examine the effects of vasoactive agents to counteract the induced hypertension. In humans, the effects of cocaine last longer than in sheep, which may, in part, be explained by the difference between the pharmacokinetics of cocaine in humans and sheep.[31] In sheep, the clearance and volume of distribution of cocaine are 3.96 l/kg and 291 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively, which are significantly higher than these values in humans (2.9 l/kg and 32.9 $ml \cdot min^{-1} \cdot kg^{-1}$).[31] This difference has been attributed to the pulmonary first-pass effect in sheep, which is not a factor in humans.[31] Thus, we administered cocaine by bolus injections every 5 min to enable us to extend the duration of increased MMAP and reduced UBF. This may represent the clinical situation with either significant cocaine abuse or abnormal metabolism.

In this study, the mean maternal and fetal cocaine concentrations achieved (fig. 1) were very high. However, these concentrations are well below those reported in cases

of cocaine intoxication in humans and suggest that the bolus administration of cocaine in this study did not produce unrealistic plasma cocaine levels. Our data suggest a maternal:fetal ratio of approximately 9:1. High maternal blood levels leading to decreased UBF appear to inhibit the placental transfer of cocaine to some degree.

Although hydralazine was administered in generous quantities (19 ± 7 mg/min), we observed no differences in fetal cardiovascular variables between the two study groups, and we assume that hydralazine does not cross the placenta in any significant amount. Although the ewes required a significantly higher hydralazine dose than humans, the effect upon the maternal blood pressure was similar to that seen in the clinical setting.

In both the control group and the treatment group, the fetal acid–base status remained statistically changed at 90 min (end of observation) from the control values, while the maternal values were similar to the control values. The cocaine was almost entirely metabolized at this point (fig. 1), but even trace amounts of cocaine affect UBF. More importantly, fetal norepinephrine levels remained elevated at 90 min, and this would contribute to altered placental circulation and fetal organ blood flow. The fetuses remained acidotic and had a significant ($P < 0.05$) decrease in P_{O_2}, suggesting a more profound effect than in the ewe. In humans, after maternal administration of cocaine, benzoylecgonine can be measured in the fetus for 4–5 days, demonstrating placental transfer and possibly impaired fetal metabolism or clearance of cocaine.[32] Fetal benzoylecgonine concentrations were still increased at the end of our study, while the cocaine concentrations declined rapidly. Prolonged benzoylecgonine concentrations may have important implications for the human fetus. It has been suggested that benzoylecgonine may be responsible for neurobehavioral changes in the cocaine-exposed newborn.[33]

In contrast to Moore *et al.*,[17] who noted an increase in norepinephrine but not epinephrine in the ewe when cocaine was administered, we observed no increase in maternal norepinephrine when cocaine alone was administered, but a significant increase in epinephrine at 15 and 30 min after administration. In the group treated with hydralazine, the maternal epinephrine and norepinephrine were significantly elevated. The latter is no doubt the result of the dynamic cardiovascular situation created by the elevated plasma cocaine levels treated with a vasodilator. To our knowledge, no one has measured the fetal catecholamine response to cocaine administration. The increases in epinephrine and particularly norepinephrine were significant and could have profound effects if they occur in the human fetus. The changes in catecholamines were no doubt enhanced by the fetal stress resulting from the decrease in UBF. The obvious acid–base changes, hypoxia, and presumed organ blood flow changes (unmeasured in this study) could have deleterious effects. Dopamine and norepinephrine are important neurotransmitters in brain development, and changes may affect neuronal development.[34] Although we did not measure central catecholamine changes in the fetus, surely they must occur in the fetus whose mother abuses cocaine, and they may be partially responsible for the long-term behavioral changes and congenital defects noted.

When interpreting the data, we recognize that one must be cautious when attempting to extrapolate animal data to clinical practice. There are several important differences between a clinical situation and the study conditions of our experiments. First, there is a species difference that must always be considered. The potential differences in the metabolism, physiologic response, distribution, and clearance of cocaine in humans *versus* animal models is of prime importance.[31] Second, administration of cocaine along with treatment does not necessarily mimic the clinical situation, in which the first step would be to stop cocaine administration. However, extraordinary plasma cocaine concentrations in humans have been documented. This may be further enhanced with decreased metabolism.[35] Third, chronic cocaine abuse during pregnancy may alter the response to cocaine and/or hydralazine, whereas our model evaluated the acute effects of cocaine in drug-naive animals. Finally, pregnancy alone has been shown to be an important variable.[30] Thus, there are a number of variables that must be taken into account when considering the effects of cocaine and potential pharmaceutical intervention.

At the inception of this study, we hypothesized that hydralazine might be a reasonable choice to treat the maternal hypertension and decreased UBF associated with cocaine intoxication. Despite the potential similarity between our study and previous attempts to control the hypertensive response to phenylephrine administration by using hydralazine, it did not improve UBF during cocaine administration. The profound catecholamine changes are no doubt an important factor. Furthermore, although hydralazine controlled maternal blood pressure adequately, the dramatic increase in heart rate of 121% could be catastrophic if it occurred in humans.

Our findings suggest that hydralazine may not be the drug of choice for the treatment of cocaine-induced hypertension in the parturient and that other vasoactive drugs might be more appropriate. Certainly, in the situation of maternal tachycardia and hypertension induced by cocaine, hydralazine—if it is to be used—should be administered especially cautiously, with particular attention paid to the maternal heart rate. We are currently investigating other possible agents in an attempt to provide better alternatives as well as to evaluate further the

mechanisms involved in the cardiovascular response to cocaine intoxication in the parturient.

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