CASE REPORT

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Tissue Distribution of Cocaine in a Pregnant Woman

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ABSTRACT: Reports of cocaine-related obstetrical problems, including abruptio placentae and spontaneous abortion, have become increasingly evident in the medical literature; however, little is known about tissue distribution of cocaine in the pregnant woman. We report the toxicologic results of distribution studies performed on a pregnant woman and her fetus. Maternal/fetal cocaine concentration ratios were high when comparing blood (9:1), brain (6:5), and kidney (10:6). Possible explanations of the mechanism for lower fetal cocaine concentrations may include uterine vasoconstriction, incomplete maternal/fetal equalibration, or rapid placental-fetal clearance.

KEYWORDS: pathology and biology, cocaine, pregnancy, tissues (biology)

The obstetrical complications associated with cocaine use include spontaneous abortion [*1*] and abruptio placentae [*1-3*], probably from drug-induced vasoconstriction and hypertension [*4,5*]. Toxic effects on the fetus may include neurologic abnormalities [*4,6*], reduced birth weight [*3*], retinopathy [*7*], and teratogenicity [*3*]. The frequency of detection of cocaine in the urine of newborn babies in South Florida [*8*] and in other locales [*9,10*] attests to its indiscriminate use by pregnant women as well as its transfer through the placenta.

We report a case in which a pregnant woman died of cocaine intoxication. The toxicologic findings show the tissue distribution of cocaine in both mother and fetus.

Case History

A 26-year-old pregnant woman was driving to a friend's party when her vehicle suddenly veered off the roadway and crashed into a row of small trees. The impact caused minor damage to the vehicle. As a witness approached the scene, the woman appeared nervous.

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She then started having convulsions and died within a few minutes. A rolled dollar bill containing white powder was found on her chest.

The victim had been a cocaine user for four years and had been enrolled in a drug rehabilitation program. She was in the second trimester of pregnancy and, other than her drug problem, did not have any illnesses.

Postmortem examination revealed a well-developed, well-nourished white woman weighing 65.8 kg (145 lb) and measuring 175.3 cm (69 in.). The only signs of external trauma were a few minor abrasions. The right side of the intact nasal septum was erythematous and coated with a tan exudate. Internal examination revealed pulmonary and visceral congestion, symmetrical cerebral swelling (brain weight, 1520 g) and an intrauterine pregnancy. There was no evidence of internal trauma. The weights of the mother's organs were: heart 250 g, right lung 630 g, left lung 490 g, liver 2160 g, spleen 310 g, right kidney 150 g, left kidney 140 g, and brain 1520 g. The gravid uterus contained a 360-g female fetus with placenta attached to the uterine apex. The amniotic fluid was cloudy, but the fetal surface of the placenta and fetal membranes were unremarkable. The umbilical cord and placenta were free of inflammation both grossly and also upon subsequent microscopic evaluation.

The following measurements were obtained from the fetus: crown-rump length 17 cm, head circumference 19 cm, chest circumference 16 cm, and abdominal circumference 13.5 cm. The fetal viscera were not weighed. However, they were of normal size, shape, and appearance. No congenital anomalies were evident. Microscopy was not performed.

Maternal and fetal blood samples were preserved with sodium fluoride and refrigerated at 0°C. Samples of brain, liver, and kidney were obtained from both mother and fetus and frozen at −20°C until analysis. Urine as well as a portion of the placenta were also collected from the mother, and cotton-tipped swabs of the nasal septum were placed in methanol. The placenta was frozen at −20°C and subsequently defrosted. Approximately 10 mL of blood were found at the bottom of the collection cup and collected for assay.

Toxicologic Analysis

The mother's urine was examined for amphetamines, barbiturates, benzodiazepines, benzoylecgonine, opiates, methadone, propoxyphene, phencyclidine, and methaqualone by the EMIT®-dau (SYVA) method in a Syva Autocarousel connected to a Gilford Stasar III spectrophotometer. EMIT data were processed by a Hewlett Packard Model HP-85 computer. In addition, the sample was analyzed for basic drugs by Toxi-Lab® thin-layer chromatography (Analytical Systems-Marion Laboratories), and spot tests for acetaminophen (*o*-Cresol reagent), ethchlorvynol (diphenylamine reagent), salicylate (Trinder's), phenothiazines (FPN), and imipramine (Forrest) were performed.

The cotton swab sample of the nasal passages was soaked in methanol until analysis. The methanol extract was then evaporated to dryness and the residue was reconstituted in EMIT buffer and analyzed by the EMIT-dau benzoylecgonine method in the same manner as a urine sample.

In a test for basic drugs, maternal blood was extracted with 1-chlorobutane as extraction solvent, using saturated borate buffer, (pH 9.2), and cyclizine as the internal standard. The extracts were evaporated to dryness under water aspirator vacuum with gentle agitation at 65°C and reconstituted in 50 μL of methanol for analysis.

Gas chromatography was performed on a Hewlett-Packard Model 5880 gas chromatograph equipped with one DB-17 and one DB-1 capillary column (30 m, 0.25-mm inside diameter, 0.25-μm film thickness). Both columns were connected to the same injection port and each terminated at a separate nitrogen-phosphorus detector. Raw data from the detectors were processed by two Hewlett Packard 5880A GC Terminals.

Four whole blood controls, each containing nine commonly encountered drugs, including cocaine at a concentration of 0.2 mg/L, are analyzed with each batch of samples to check

relative retention time calibrations and to calculate estimates of drug concentrations so that appropriate sample dilutions can be used for subsequent quantification. In addition, a whole blood negative control is analyzed with each batch.

The extract remaining from the gas chromatographic blood basic drug test was analyzed by gas chromatography/mass spectrometry (GC/MS) to confirm positive findings. The Finnigan Model 4510 gas chromatograph/mass spectrometer was operated in the electron impact mode scanning from *m/z* 45 to 400. A 15-m DB-5 capillary column (0.25-mm inside diameter, 0.25-μm film, J & W) was used with the following GC program: 50°C for 2 min, followed by an 18-min ramp to 300°C with a hold of 5 min.

Alcohol screening was performed by headspace gas chromatography on a Perkin-Elmer Sigma 2000 GC with a HS-1 automated headspace sampler. The sample was split into two capillary columns (DB-17 and DB-Wax from J & W) each 30 m in length and 0.25-mm inside diameter with a 0.25-μm film thickness. The GC was operated isothermally at 45°C. Components were detected by dual flame ionization detectors and detector signals were processed by a Concurrent 3203 computer using Perkin-Elmer CLAS software.

Quantitative analyses of cocaine in blood and solid tissues were performed by gas chromatography using nitrogen-selective detection. The stock solutions of standards were prepared at concentrations of 1 mg/mL as the free base. The cocaine stock solution was prepared in dimethyl formamide (DMF), while the cyclizine (internal standard) stock solution was prepared in methanol. The working standard solution for cocaine was freshly prepared at 10 mg/L in water prior to each assay and was spiked into fluoride-preserved drug-free whole blood to yield blood standard concentrations of 0.00, 0.10, 0.50, and 2.0 mg/L. Cyclizine internal standard working solution was prepared at 0.5 mg/L in water.

In a screw-top test tube, 1 mL of blood, 2 g of a 1 : 1 tissue homogenate in water, or 1 mL of standard were added to 1 mL of internal standard with 1 mL of saturated borate buffer, pH 9. The contents of the tube were vortexed briefly and 10 mL of 1-chlorobutane were added to each tube. The tubes were tightly capped and placed on a rotary mixer for 10 min. They were then centrifuged for 10 min, and the 1-chlorobutane was transferred to a second screw-top test tube containing 1.5 mL of 1.0*N* hydrochloric acid. These tubes were capped and placed on the rotary mixer for 10 min, centrifuged, and the 1-chlorobutane layer was discarded. The acid layer was washed with 5 mL of hexane by mixing and centrifuging and the hexane layer was discarded. The aqueous layer was then saturated with a 1 : 1 (mole/mole) mixture of sodium bicarbonate/sodium carbonate, and 2 mL of saturated borate buffer were added. The contents of the tubes were vortexed, and 10 mL of 1-chlorobutane were added. At this point, the tubes were again rotated and centrifuged, and the organic layer was transferred to disposable test tubes and evaporated to dryness in a vortex evaporator under water aspirator vacuum at 60°C. The extracts were reconstituted in 50 μL of methanol, of which 1.0 μL was injected onto a 15-m DB17 (J & W) megabore column (0.53-mm diameter, 1.0-μm film thickness) in a Perkin-Elmer 8420 gas chromatograph equipped with a nitrogen-phosphorus detector. The temperature program consisted of the following parameters: initial temperature 200°C for 2 min, 10 min to 270°C, hold for 2 min. Cocaine concentrations were calculated using a Concurrent Model 3203 computer with Perkin-Elmer CLAS software. Analyses were performed in duplicate and results were averaged. Samples with cocaine concentrations greater than the 2.0-mg/L high standard were diluted with deionized water and reanalyzed.

Results and Discussion

Toxicologic examination of the mother's urine revealed only cocaine and the cocaine metabolite, ecgonine methyl ester. Interestingly, the EMIT-benzoylecgonine analysis of the urine was below that of the low (300 ng/mL) calibrator. Cocaine was detected in the nasal swabs and blood of the mother.

TABLE 1—*Cocaine concentrations.*

Source	Mother	Fetus	Maternal : Fetal Ratios
Blood	13.7 mg/L	1.5 mg/L[a]	9:1[b]
Brain	29.3 mg/kg	4.5 mg/kg	6:5
Liver	1.34 mg/kg	0.87 mg/kg	1:5
Kidney	14.6 mg/kg	1.37 mg/kg	10:6
Nasal swabs	detected[c]		
Urine	detected[c]		

[a]This is an estimated value since the limited amount of fetal blood precluded rigorous quantification.

[b]Based upon estimated fetal blood concentration.

[c]No quantitation performed.

Table 1 lists the cocaine concentrations for both mother and fetus. The maternal blood cocaine concentration (13.7 mg/L) is over twice the average detected in deaths from cocaine toxicity [*11,12*]. Baselt reported an average blood concentration of 5.2 mg/L (range: 0.9 to 21 mg/L) based on 18 fatal cases [*11*], whereas our office reported 26 such deaths with an average of 6.2 mg/L (range: 0.1 to 20.9 mg/L) [*12*]. Based upon the circumstances of death, autopsy findings, and the blood concentration of cocaine, it was concluded that the cause of death was cocaine intoxication and the manner of death was accident.

Information regarding tissue distribution of cocaine has been scant in the medical literature. However, brain, spleen, kidney, and urine are known to concentrate cocaine at higher levels than the blood [*11.13-18*]. In this case, cocaine concentrations were higher in the mother's brain and kidney, than in the blood.

The limited amount of fetal blood precluded rigorous quantitation. Therefore, the concentration of cocaine in fetal blood, approximately 1.5 mg/L, was determined by comparing the analytical result with a 0.2-mg/L cocaine control analyzed along with the samples in the gas chromatographic drug examination. Analysis of fetal brain, liver, and kidney revealed substantial concentrations of cocaine in these organs as well (Table 1).

The high maternal/fetal cocaine concentration ratios (Table 1) have also been reported from toxicologic studies on pregnant mice where fetal brain and liver concentrations were one third and one quarter of the respective levels in the maternal organs [*19*]. The lower fetal concentrations may be the result of cocaine-induced vasoconstriction reducing blood flow to the gravid uterus. Supporting this contention are animal experiments with pregnant ewes which have demonstrated prominent decreases in uterine blood flow upon infusion of norepinephrine [*20*] or cocaine [*21*]. An alternative explanation is that the mother's death occurred so rapidly following absorption of the drug that the pharmacokinetic compartment represented by the fetus was not at equilibrium with the maternal blood. Hence, when maternal circulation ceased, so did placental transfer. Drug distribution studies in pregnant animals have disclosed high maternal/fetal plasma concentration ratios for meperidine (3.3 [*22*]), methadone (2 to 5 [*23*], 2.9 [*24*]), and morphine (7.6 [*24*]). To our knowledge, this is the first such assay of cocaine in the human fetus. Placental and fetal clearances of cocaine probably play a role in the maternal/fetal ratios as with other drugs [*25*].

Toxicologic analysis of the blood associated with the placenta revealed a relatively low value (2.9 mg/L) when compared with maternal blood (13.7 mg/L), brain (29.3 mg/kg), and kidney (14.6 mg/kg). Since the placenta is a vascular organ, this concentration may be reflective of the fetal blood concentration. Maternal blood would probably not increase the placental concentration since most would be vacated from the placenta after separation at autopsy. There was no evidence of adherent maternal blood clots along the maternal surfaces of the placenta.

If the reduced fetal cocaine concentrations in this case reflect the drug-induced vasoconstriction and decreased uterine blood flow, the tendency towards spontaneous abortions in cocaine-using mothers is more understandable. Additional toxicologic data from animal studies and from medical examiner/coroner cases may help elucidate the effects of cocaine during pregnancy.

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References

[1] Chasnoff, I. J., Burns, W. J., Schnoll, S. H., and Burns, K. A., "Cocaine Use in Pregnancy," *New England Journal of Medicine*, Vol. 313, No. 11, Sept. 1985, pp. 666-669.

[2] Acker, D., Sachs, B. P., Tracey, K. J., and Wise, W. E., "Abruptio Placentae Associated with Cocaine Use," *American Journal of Obstetrics and Gynecology*, Vol. 146, No. 2, May 1983, pp. 220-221.

[3] Bingol, N., Fuchs, M., Diaz, V., Stone, R. K., and Gromish, D. S., "Teratogenicity of Cocaine in Humans," *Journal of Pediatrics*, Vol. 110, No. 1, Jan. 1987, pp. 93-96.

[4] Smith, J. E. and Deitch, K. V., "Cocaine: A Maternal, Fetal and Neonatal Risk," *Journal of Pediatric Health Care*, Vol. 1, No. 3, May/June 1987, pp. 120-124.

[5] Cregler, L. L. and Mark, H., "Medical Complications of Cocaine Abuse," *New England Journal of Medicine*, Vol. 315, No. 23, Dec. 1986, pp. 1495-1500.

[6] Le Blanc, P. E., Parekh, A. J., Naso, B., and Glass, L., "Effects of Intrauterine Exposure to Alkaloidal Cocaine ('Crack') (Letter)," *American Journal of Diseases of Children*, Vol. 141, No. 9, Sept. 1987, pp. 937-938.

[7] Teske, M. P. and Trese, M. T., "Retinopathy of Prematurity-like Fundus and Persistent Hyperplastic Primary Vitreous Associated with Maternal Cocaine Use (Letter)," *American Journal of Opthalmology*, Vol. 103, No. 5, May 1987, pp. 719-720.

[8] Hall, J. H., "Impact of Mother's Cocaine Use," *Street Pharmacologist* (Up Front, Inc.), Vol. 11, No. 10, Oct. 1987, p. 1.

[9] Madden, J. D., Payne, T. F., and Miller, S., "Maternal Cocaine Abuse and Effect on the Newborn," *Pediatrics*, Vol. 77, No. 2, Feb. 1986, pp. 209-210.

[10] Oro, A. S. and Dixon, S. D., "Perinatal Cocaine and Methamphetamine Exposure: Maternal and Neonatal Correlates," *Journal of Pediatrics*, Vol. 111, No. 4, Oct. 1987, pp. 571-577.

[11] Baselt, R. C., *Disposition of Toxic Drugs and Chemicals in Man*, Biomedical Publications, Davis, CA, 1982, pp. 193-198.

[12] Mittleman, R. E. and Wetli, C. V., "Death Caused by Recreational Cocaine Use," *JAMA*, Vol. 252, No. 14, Oct. 1984, pp. 1889-1893.

[13] Poklis, A., Maginn, D., and Barr, J. L., "Tissue Disposition of Cocaine in Man: A Report of Five Fatal Poisonings," *Forensic Science International*, Vol. 33, No. 2, Feb. 1987, pp. 83-88.

[14] Poklis, A., Mackell, M. A., and Graham, M., "Disposition of Cocaine in Fatal Poisoning in Man," *Journal of Analytical Toxicology*, Vol. 9, No. 5, Sept./Oct. 1985, pp. 227-229.

[15] Lundberg, G. D., Garriott, J. C., Reynolds, P. C., Cravey, R. H., and Shaw, R. F., "Cocaine-Related Death," *Journal of Forensic Sciences*, Vol. 22, No. 2, April 1977, pp. 402-408.

[16] Di Maio, V. J. M. and Garriott, J. C., "Four Deaths due to Intravenous Injection of Cocaine," *Forensic Science International*, Vol. 12, No. 2, Sept./Oct. 1978, pp. 119-125.

[17] Bednarczyk, L. R., Gressman, E. A., and Wymer, R. L., "Two Cocaine-Induced Fatalities," *Journal of Analytical Toxicology*, Vol. 4, No. 5, Sept./Oct. 1980, pp. 263-265.

[18] Spiehler, V. R. and Reed, D., "Brain Concentrations of Cocaine and Benzoylecgonine in Fatal Cases," *Journal of Forensic Sciences*, Vol. 30, No. 4, Oct. 1985, pp. 1003-1011.

[19] Shah, N. S., May, D. A., and Yates, J. D., "Disposition of Levo-[3H] Cocaine in Pregnant and Nonpregnant Mice," *Toxicology and Applied Pharmacology*, Vol. 53, No. 2, April 1980, pp. 279-284.

[20] Rosenfeld, C. R. and West, J., "Circulatory Response to Systemic Infusion of Norepinephrine in the Pregnant Ewe," *American Journal of Obstetrics and Gynecology*, Vol. 127, No. 4, Feb. 1977, pp. 376-383.

[21] Woods, J. R., Plessinger, M. A., and Clark, K. E., "Effect of Cocaine on Uterine Blood Flow and Fetal Oxygenation," *JAMA*, Vol. 257, No. 7, Feb. 1987, pp. 957-961.

[22] Szeto, H. H., Mann, L. I., Bhakthavathsalan, A., Liu, M., and Inturrisi, C. E., "Meperidine Pharmacokinetics in the Maternal Fetal Unit," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 206, No. 2, Aug. 1978, pp. 448-459.

[23] Szeto, H. H., Clapp, J. F., III, Larrow, R. W., Hewitt, J., Inturrisi, C. E., and Mann, L. I., "Disposition of Methadone in the Bovine Maternal-Fetal Unit," *Life Sciences*, Vol. 28, No. 19, May 1981, pp. 2111-2117.

[24] Szeto, H. H., Umans, J. G., and McFarland, J., "A Comparison of Morphine and Methadone Disposition in the Maternal-Fetal Unit," *American Journal of Obstetrics and Gynecology*, Vol. 143, No. 6, July 1982, pp. 700-706.

[25] Braude, M. C., Szeto, H. H., Kuhn, C. M., Bero, L., Ignar, D., et al., "Perinatal Effects of Drugs of Abuse," *Federation Proceedings*, Vol. 46, No. 7, May 1987, pp. 2446-2453.

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