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Vitreous Humor Cocaine and Metabolite Concentrations: Do Postmortem Specimens Reflect Blood Levels at the Time of Death?

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ABSTRACT: The interpretation of postmortem cocaine concentrations is made in an attempt to estimate drug concentrations present at the time of death and thus infer not only drug presence but drug toxicity. Previous data suggest that changes in postmortem blood cocaine concentrations over time are not predictable and interpretation of cocaine levels should be done with caution. However, these data come from autopsy case series where vital information, such as blood cocaine concentration at the time of death, dose and time since last use, and postmortem interval is often not known. The purpose of this study was to characterize postmortem changes in cocaine and metabolite concentrations relative to premortem concentrations over time at two anatomic sites: peripheral blood and vitreous humor, in a controlled, large animal model. Juvenile swine were given cocaine HCl 10 mg/kg as an IV bolus which resulted in seizures and wide complex tachycardia. Five minutes after cocaine administration, animals were euthanized. At time of death and eight hours postmortem, femoral venous blood and vitreous humor (VH) samples were obtained for quantitation of cocaine, benzoyl ecgonine (BE), and ecgonine methyl ester (EME) by GC/MS. There were no significant increases over time in mean femoral vein concentrations of cocaine or BE. However, a large interanimal variability in direction and magnitude of concentration changes was seen. Mean EME concentrations at the femoral site increased significantly over 8 hours ($P < 0.03$). Mean VH cocaine concentrations at time of death were significantly lower than corresponding blood concentrations ($P < 0.02$). However, 8 hour postmortem VH cocaine concentrations increased in all animals and were similar to the femoral blood concentrations at time of death. These results emphasize the variability in postmortem cocaine concentrations and the need to consider the site of collection and postmortem interval as variables in interpreting postmortem cocaine and metabolite concentrations relative to premortem values.

KEYWORDS: toxicology, postmortem interval, cocaine, benzoyl ecgonine, ecgonine methyl ester, blood drug concentrations, blood collection sites, forensic medicine, postmortem changes, vitreous humor, femoral vein

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The extrapolation of postmortem drug concentrations to concentrations at the time of death, and ultimately to drug effect at the time of death, is a complex and problematic issue for the pathologist or toxicologist. There is a limited amount of published data, mostly in the form of small case series, relating to this problem. Variables such as dosage, phase of distribution and elimination, clinical findings, and time of death are often unknown, making interpretation of these data difficult.

The phenomenon of postmortem drug release has been described for a number of drugs [*1–14*]. Postmortem release of drug from tissues with higher drug concentrations to surrounding tissues can result in concentration changes with respect to site as well as time of collection. Thus, it has been recommended that blood specimens be obtained from an isolated peripheral site such as the femoral vein as soon as possible after death to minimize postmortem release, although this has not been prospectively validated for the vast majority of drugs [*6,15*].

The interpretation of postmortem cocaine and cocaine metabolite concentrations is further complicated by cocaine's metabolism. In vivo, the majority of cocaine is metabolized to ecgonine methyl ester (EME) by plasma and liver esterases, and to benzoyl ecgonine (BE) by spontaneous hydrolysis [*16*]. There is also some evidence that enzymatic degradation to benzoyl ecgonine may occur [*17*]. Spontaneous hydrolysis would be expected to continue after death and has been demonstrated to occur in stored samples [*16–21*]. Hydrolysis is inhibited to some extent by acid pH and lower temperatures, conditions which occur after death [*19,20*]. Enzymatic degradation may also continue after death or in vitro, unless inhibited by lower temperatures, cholinesterase inhibitors or sodium fluoride [*19,20*]. Thus, it would be expected that cocaine concentrations would decline after death secondary to continued nonenzymatic hydrolysis and perhaps to continued enzymatic activity as well.

Cocaine has an apparent volume of distribution of approximately 2 L/kg [*16*]. This volume of distribution indicates a relatively large amount of extravascular drug which might serve as a depot for postmortem release. That redistribution of cocaine into the vascular compartment may indeed occur is suggested by observed increases in postmortem blood and vitreous humor concentrations described in autopsy case series [*1,22*]. However, in these studies, a great

variability in both the magnitude and direction of changes in cocaine and metabolite concentration over time was noted. There are no data relating site and time dependent postmortem cocaine, BE, and EME concentration changes to concentrations at the time of death.

The purpose of this study was to determine the relationship of postmortem vitreous humor and femoral blood cocaine and metabolite concentrations to perimortem femoral blood concentrations in a large animal model.

Methods

Nine chronically instrumented juvenile Hampshire swine (weight 13.4–20 kg) were housed at 22–24°C, with a 12 hour light/dark cycle, in the institutional animal care facility at Denver General Hospital. Animals were fed a standard diet of pig chow with free access to water. All animals had previously received 8 doses of IV cocaine HCl 10 mg/kg over not less than three weeks as part of another protocol (*23,24*) with at least a 48-hour washout before the current study. The study was approved by the Animal Use in Research Committee of the Denver General Hospital.

Prior to the experiment, a serum sample was obtained to confirm that residual cocaine or metabolites were not detectable from previous experiments. Animals then received cocaine HCl 10 mg/kg in 4 cc normal saline through an indwelling intrajugular catheter, followed by a 2 cc saline flush. Five minutes after cocaine administration, animals were killed with 450 mg pentobarbital IV push. Death was confirmed by asystole on a cardiac monitor and absence of pulse. Within three minutes of death, femoral blood and vitreous humor specimens were obtained. Femoral samples were obtained by needle aspiration from the femoral vein under direct visualization after limited dissection. While samples were being collected, the proximal vein was occluded to prevent aspiration of the sample from the contiguous central blood pool. Animals were then placed in a left lateral decubitus position at 24°C for the duration of the experiment. A second vitreous and femoral sample was collected eight hours postmortem. A limited thoracotomy was performed to aspirate blood from the left ventricle. Heart blood and urine samples were collected at time of death, 2, 4, and 8 hours postmortem, and are presented in a separate report [*25*]. Samples were treated with calcium oxalate, sodium fluoride, and centrifuged. The supernatant was then decanted, pH adjusted to 5.5 with 10% acetic acid and the specimen was frozen at −20°C within 30 minutes of collection. Specimens were assayed within 60 days of collection.

Reagents and Standards

All inorganic compounds were reagent grade. Solvents were high performance liquid chromatography grade. Cocaine HCl, benzoylecgonine, and ecgonine methyl ester and their deuterated counterparts were purchased from Alltech-Applied Science. Cocaine and metabolite reference materials were used to prepare a tertiary standard solution containing 10 mcg drug/mL methanol. For each sample batch, the working cocaine and metabolite calibrator preparation was added to blood or serum to yield final concentrations of 0, 150, 500, 1000, 2000, and 5000 ng/mL. The derivatization reagent consisted of pentafluoroproprionic anhydride (Pierce, product 65193). Working internal standards were prepared using deuterated cocaine, benzoyl ecgonine and ecgonine methyl ester in methanol to produce a solution containing 10 mcg drug/mL.

Extraction Procedure

Two mL of sample were mixed with 3 mL chloroform, 1 gram of 1:1:12 Na_2CO_3, $NaHCO_3$, NaCl buffer, 500 microliters of working combination internal standard, 2 mL water, 100 microliters 10% zinc sulfate, and 0.33 mL isopropanol in a 16 × 100 mm extraction tube. The mixture was rocked for 5 minutes, then centrifuged at 2000 rpm for 5 minutes. The aqueous phase was aspirated to waste, 1 mL water was added, and the preparation was rocked for 5 minutes, centrifuged at 2000 rpm for 5 minutes and the aqueous phase again aspirated and discarded. The organic phase was decanted to a 5 mL reaction vial and one drop 0.1 N HCl was added to form HCl salts and reduce loss of volatile free base analytes. The mixture was then evaporated to dryness under a stream of nitrogen at 75°C.

Derivatization

The residue was treated with 25 microliters of pentafluoropropanol and 50 microliters of pentafluoroproprionic anhydride, capped and incubated at 75°C for 15 minutes. The mixture was evaporated to dryness under nitrogen at 75°C. The residue was reconstituted with 100 microliters ethyl acetate. One microliter of the residue was injected into a Hewlett Packard 5970 MSD gas chromatograph/mass spectrometer in the selected ion monitoring mode, equipped with a 15 m capillary column (J&W DB-1 #122-1032). The column temperature was programmed at 90–280°C at 32–20°C per minute. Ions monitored were cocaine: 82, 182, 303.3; deuterated cocaine: 85, 185, 306; benzoyl ecgonine: 82, 272, 421; deuterated benzoyl ecgonine: 85, 275, 424; ecgonine methyl ester: 182, 314, 345, and deuterated ecgonine methyl ester: 185, 317, 348. Limits of quantitation for cocaine and measured metabolites using this method was 200 ng/mL.

Plasma cholinesterase was measured following the method of Michael et al. [*26*] with a normal human range of 0.44–1.40 delta pH/h.

Statistics

Raw data are provided to illustrate patterns of change between site and over time in individual animals. Ratios of change compared to baseline femoral drug concentrations are shown for each animal. Also, mean femoral cocaine and metabolite concentrations at the time of death were compared to 8 hour postmortem femoral samples and vitreous humor samples (both time of death and 8 hour postmortem) using a paired students t-test with a significant P defined as less than 0.05 (Statistix ver 4.0, statistical software).

Results

Prior to cocaine administration, cocaine and metabolite concentrations were below the limits of detection for all animals. After injection of cocaine, all animals experienced tonic clonic seizure activity and wide complex tachycardia which persisted until euthanasia at 5 minutes after injection. Mean femoral blood pH (n = 3) at time of death was 6.89 ± 0.39 and at 8 hours postmortem was 6.11 ± 0.14. Mean plasma cholinesterase activity in femoral blood (n = 3) just prior to drug administration was 0.17 ± 0.03 delta pH/h [*26*].

Femoral blood and vitreous humor concentrations of cocaine, BE and EME for each animal are shown in Table 1.

Femoral blood samples at time 0 represent peripheral blood concentrations at the time of death. All comparisons are made

TABLE 1—*Femoral blood and vitreous humor cocaine, BE, and EME concentrations at time of death and 8 hours postmortem for individual animals*

Time 0		Femoral		Vitreous Humor		
Pig	Cocaine	EME	BE	Cocaine	EME	BE
1	1265	570	lod	1117	lod	lod
2	1730	2093	lod	507	lod	lod
3	m	m	m	1228	lod	lod
4	m	m	m	m	m	m
5	6774	984	lod	386	255	lod
6	3414	698	lod	646	lod	lod
7	5026	263	lod	206	lod	lod
8	3820	113	lod	m	228	m
9	685	106	lod	2484	383	lod
mean	**3245**	**690**	**lod**	**939**	**109**	**lod**
Eight hours postmortem						
1	1769	1309	lod	3244	459	lod
2	1374	1595	211	2274	279	lod
3	2619	3475	lod	5187	475	lod
4	7780	1536	966	3154	1080	904
5	1341	1248	571	1407	279	lod
6	5055	2639	416	2661	285	lod
7	6860	931	lod	3736	lod	lod
8	1520	660	lod	m	1228	689
9	3797	1347	lod	2875	575	lod
mean	**3568**	**1637**	**240**	**3067**	**518**	**177**

NOTE: For calculation of mean, set lod = 0. All data in ng/mL. m = Data not available.
lod = Limits of detection.

with respect to this specimen. Figures 1, 2, and 3 show cocaine, BE, and EME concentrations at time of death compared to 8 hours postmortem. There was no significant change in mean cocaine or BE concentrations at the femoral vein site between the time of death and 8 hours postmortem. However, mean femoral EME concentrations increased more than 2 fold during the same time period ($P < 0.03$).

As shown in Fig. 1, vitreous humor cocaine concentrations were significantly lower than femoral specimens at the time of death ($P < 0.02$). However, by 8 hours postmortem, mean vitreous humor cocaine concentrations rose (939 ± 777 to 3067 ± 1106 ng/mL, $P < 0.001$) to a value similar to that seen in femoral samples at the time of death ($P < 0.84$). There were no significant differences between femoral BE and EME concentrations at time

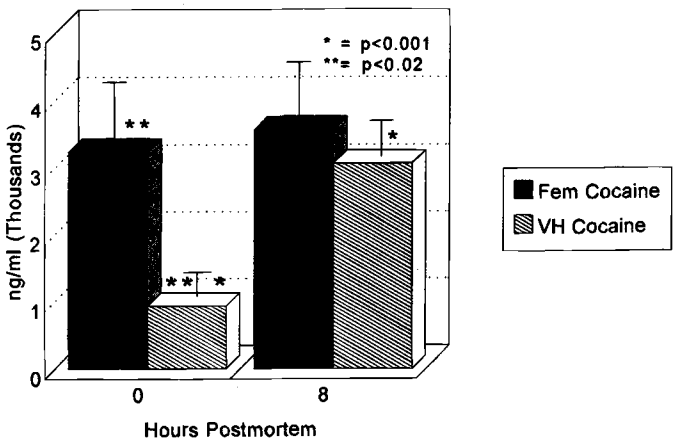

FIG. 1

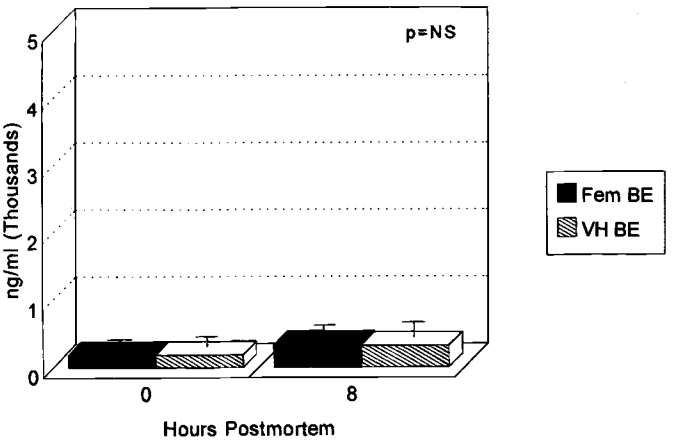

FIG. 2

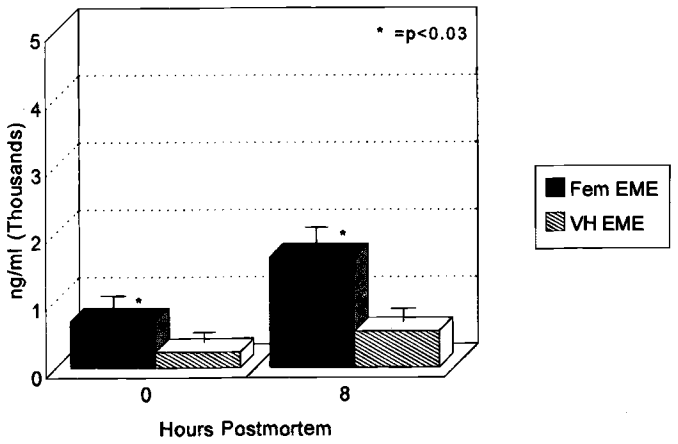

FIG. 3

of death and vitreous humor BE and EME concentrations at time of death or 8 hours postmortem.

Table 2 shows the ratio of change in drug concentrations over time for each animal compared to the drug concentration measured in the femoral vein at time of death. Femoral vein cocaine concentrations increased over time in 4 animals and decreased in 3 animals (range 0.2–5.5 fold). Note that despite a lack of a statistically significant change in the means of femoral cocaine concentrations over time, there was great interanimal variability in both the magnitude and the direction of change over the postmortem interval, even in these controlled conditions. This variability in direction of change of cocaine concentrations was noted for all comparisons except vitreous humor. Vitreous humor showed a consistent increase in cocaine concentration over the 8 hour postmortem interval in all animals (range 1.2 to 18 fold).

Benzoyl ecgonine concentrations were below the limits of detection for the majority of samples; therefore, ratios are not calculated for this metabolite. Ecgonine methyl ester concentrations increased consistently over 8 hours at the femoral site, with ratios greater than 1 in 6 of 7 animals (range 0.8 to 12.7 fold). Eight hour vitreous humor EME: femoral EME ratios were less than 1 in 5 of 7 animals (range 0.1 to 10.9 fold).

TABLE 2—*Ratio of change of cocaine and EME concentrations in vitreous humor and postmortem femoral blood concentrations compared with femoral vein concentrations at the time of death for individual animals.*

Pig	Ratio Cocaine F8:F0	V0:F0	V8:F0
1	1.4	0.9	2.6
2	0.8	0.3	1.3
3	m	m	m
4	m	m	m
5	0.2	0.1	0.2
6	1.5	0.2	0.8
7	1.4	0.04	0.7
8	0.4	m	m
9	5.5	3.6	4.2
	Ratio EME		
1	2.3	0.4	0.8
2	0.8	0.1	0.1
3	m	m	m
4	m	m	m
5	1.3	0.3	0.3
6	3.8	0.3	0.4
7	3.5	0.8	0.8
8	5.8	2	10.9
9	12.7	3.6	5.4

F0 = femoral blood sample time of death
F8 = femoral blood sample 8 hours postmortem
V0 = vitreous humor sample time of death
V8 = vitreous humor sample 8 hours postmortem
m = data not available

Discussion

There is a paucity of data describing changes in drug concentrations in the body after death. Existing data consists mainly of autopsy case series data and a limited number of controlled animal experiments. In most forensic studies, however, parameters including dose, route and time of drug administration, and postmortem interval are not described. These variables are crucial in determining not only the relationship between antemortem and postmortem concentrations, but also in delineating the mechanisms involved in postmortem changes in drug concentrations. The use of a large animal model to evaluate postmortem pharmacokinetics allows control of these variables, and provides a model for examining mechanisms involved in postmortem drug release.

Cocaine presents an especially difficult challenge for the forensic toxicologist because of its metabolism. On one hand, cocaine concentrations in forensic specimens might be expected to decrease due to continued spontaneous hydrolysis and enzymatic degradation. On the other hand, an increase in cocaine concentrations might be expected secondary to release from tissue stores. Decline of cocaine concentrations over time in stored blood is well described [*20*]. Cocaine concentrations of 1000 ng/mL in stored blood declined by more than 20% after 24 hours. This decline was slowed by the addition of fluoride, pH adjustment to 5, and refrigeration at 4°C [*20*]. In this animal model, the temperature drop to ambient (25°C) and relative acidosis (pH 6.11 at eight hours after death), would be expected to slow postmortem cocaine metabolism. Premortem plasma cholinesterase activity in this study was low compared to human normal values. This lower cholinesterase activity compared to human values might also be expected to result in a lower than expected rate of postmortem cocaine metabolism to EME and possibly BE. Postmortem samples were not assayed for cholinesterase activity. Thus, based on knowledge of cocaine's metabolism and in vitro stored sample degradation, some degree of continued cocaine degradation would be expected even in the relative hypothermic, acidotic conditions associated with putrefaction in this experiment.

With an apparent volume of distribution greater than that of total body water (2 L/kg), it would be expected that there are increased concentrations of cocaine in extravascular spaces with concentration gradients that would favor postmortem release into the vascular compartment. Postmortem release is supported by data from Beno and Kriewall [*22*] who found in an autopsy case series that vitreous humor cocaine concentrations increased as much as 330% over a 19 hour interval. Hearn et al. [*1*], in another autopsy case series, examined cocaine concentrations with respect to site and time of collection and found that cocaine concentrations usually increased over time after death in heart, aorta, and femoral vein, but decreased in subclavian blood. However, a great variability in magnitude and also direction of change was noted at each collection site. From these results, Hearn concluded that it was difficult to correlate postmortem cocaine concentrations with premortem values. In both of these studies, chronicity of use, dose, route of administration, postmortem interval, and most importantly, antemortem concentrations were not known in the majority of cases.

In this model, animals were bolused with a large cocaine dose and sacrificed at 5 minutes after drug administration. Therefore, high blood concentrations of cocaine were observed, with probable incomplete distribution to vitreous humor and other extravascular compartments. Because of the short period of time between drug bolus and death, it would be expected that a relatively small amount of cocaine would be available for postmortem redistribution from extravascular sites to the vascular compartment. There was no significant change in mean cocaine concentration over time at the femoral vein, suggesting that postmortem release is not important at this site in the conditions of this experiment. Given some degree of expected degradation, it is possible that postmortem release occurred, but ongoing postmortem metabolism resulted in no net change in mean cocaine concentration at this site. Frequently, postmortem drug release data is analyzed by comparing change over time to baseline values for each individual subject. It is important to note that despite the lack of a statistically significant change in mean femoral vein cocaine concentrations over an 8 hour postmortem interval, increases were noted in 4 animals and decreases were noted in 3 animals with a range of premortem: postmortem ratios of 0.2–5.5. Even in this study where dose, time of death and postmortem interval were identical, this great variability in even the direction of change over time underscores the caution that should be exercised in interpreting postmortem blood cocaine concentrations in each individual case.

In vitreous humor, mean cocaine concentrations were low compared to femoral vein concentrations at the time of death. This probably represents incomplete distribution into the vitreous at the time of sacrifice. Vitreous humor cocaine concentrations then increased significantly and consistently over 8 hours after death. The mean cocaine concentration at 8 hours in the vitreous humor appears to be similar to femoral vein concentration at the time of death. The failure to detect a difference here may reflect a beta error. Post hoc power calculations show that to detect the observed difference between these two samples with an alpha of 0.05 and beta of 0.8 would require a sample size of 165. Thus, it is possible that vitreous humor concentrations at 8 hours do not exactly reflect those at the time of death,

however any undetected difference would likely be small. Since we did not study any later time points, it is not known if vitreous humor cocaine concentrations would have continued to rise or would have equilibrated. While some increase in vitreous humor drug concentration was expected due to diffusion from periorbital blood, which presumably has a higher cocaine concentrations, the magnitude of this increase was unexpected. Vitreous humor is well isolated from the central body cavity and is exposed to a relatively small blood volume at a given time. Thus, the complete equilibration of VH and measured blood cocaine concentrations would seem unlikely. It is also possible that other intraocular tissue such as retina might act as a depot for cocaine release, but this has not been demonstrated.

Although VH cocaine concentrations consistently increased after death in each animal, the ratio of femoral blood cocaine concentrations at time of death to vitreous samples at 8 hours postmortem for each animal again showed a large variability in direction and magnitude of change. Relative to femoral blood, 8 hour VH cocaine concentrations increased in 3 animals and decreased in 3 animals (range 0.2–4.2). Thus, the fact that 8 hour VH mean cocaine concentrations were not statistically significantly different from femoral vein concentrations at the time of death should not be interpreted as indicating that VH is a reliable specimen for measuring postmortem cocaine concentrations. It is not known whether vitreous samples at a later postmortem interval would continue to rise.

The pattern of metabolites observed was unexpected. Very little BE was measured even at 8 hours postmortem and, for most samples, BE was below the limits of detection at all times. The relative acidosis and hypothermia of death may have inhibited cocaine hydrolysis; however this pattern was also noted in live animals [*23,24*]. The lack of BE formation in this model is unexpected and has no ready explanation, as most investigators feel that spontaneous nonenzymatic hydrolysis is responsible for its formation. Some enzymatically mediated degradation to BE may occur as well [*17*]. It is possible that the relatively acidotic and hypothermic conditions occurring after death inhibited degradation to BE more than to EME. Ecgonine methyl ester increased over time after death as expected. Other cocaine metabolites were not measured.

Summary

In this controlled, large animal model of acute IV cocaine intoxication, there was no statistically significant change in mean cocaine or BE concentrations over an 8 hour postmortem interval at the femoral site. Perimortem vitreous humor cocaine concentrations were significantly lower than perimortem femoral concentrations. By the end of an 8 hour postmortem interval, however, VH cocaine concentrations significantly increased and were not significantly different from perimortem femoral concentration. However, the pattern of change in cocaine concentrations was highly variable even in these controlled conditions, underscoring the caution that should be exercised in extrapolating postmortem cocaine concentrations to antemortem values.

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