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ORIGINAL COMMUNICATION

Cocaine metabolism in hyperthermic patients with excited delirium

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SUMMARY. The half-life of cocaine in clinical experiments has been reported to range from 60 to 90 min. It has been previously suggested that elevated temperature may accelerate the metabolism of cocaine. However, there is no clinical data to indicate the presence of hyperthermia like that seen in excited delirium alters the half-life of cocaine. We report the results of half-life determinations from serial cocaine concentrations in two patients with excited delirium. Both patients presented to the emergency department with classic findings of excited delirium that included hyperthermia, agitation, and cardiovascular aberrations. One patient died despite aggressive therapeutic intervention. Cocaine and metabolite concentrations were determined by an extractive alkylation mass spectrometry procedure. Presenting cocaine concentrations in patient 1 and patient 2 were 0.387 and 0.266 mg/L respectively. Results from pharmacokinetic modeling of the serial concentrations show that the half-life of cocaine was not significantly accelerated, despite the presence of hyperthermia. Data from these two cases provide further evidence that catastrophic reactions to cocaine are independent of amount or route of administration, and that the metabolism of cocaine, at least in these patients, was not altered by hyperthermia.

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INTRODUCTION

Concentration ranges of cocaine in the blood of recreational drug users dying of trauma are indistinguishable from those observed in cases where death is clearly due to cocaine toxicity.[1] This overlap, no doubt, explains why a relationship between post-mortem cocaine blood concentration and toxicity has yet to be established.[2–4] Nowhere is this lack of relationship more evident than in the subset of cocaine-related deaths from excited delirium. This syndrome, characterized by hyperthermia, delirium with agitation, respiratory arrest, and death, is invariably associated with low-to-modest blood cocaine concentrations.[5–6] Until recently, there was no plausible explanation for this finding.

Data from recent in-vitro studies have shown that elevated temperatures accelerate the breakdown of cocaine.[7] Since the average patient with excited delirium has a temperature of above 40°C (104°F) at the time of first medical encounter,[6] and since most of these deaths tend to occur in the summer months,[8] temperature accelerated metabolism might explain the surprisingly low blood-cocaine concentrations usually detected at autopsy, although clinical confirmation remains wanting.

The effects of temperature on the pharmacokinetics of cocaine in the living have not been studied and ethical considerations prohibit any controlled studies utilizing doses of cocaine comparable to those self-administered by the drug-abusing population.

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Measurements of cocaine concentrations in the two hyperthermic cocaine abusers with excited delirium suggest that in the living, the half-life of cocaine is not significantly altered by elevated body temperature.

MATERIAL AND METHODS

The two patients described here were part on an ongoing study approved by the institutional review board of the University of Tennessee College of Medicine.

All data were collected prospectively. After the initial evaluation by one of the investigators, 10 cc of blood was drawn and placed in a vaccutainer tubes containing sodium fluoride and frozen immediately. Multiple samples for time series determination of cocaine and its major metabolites were drawn at varying intervals during the first 12 h after presentation. Samples were shipped to the collaborating laboratory on dry ice.

Determination of cocaine and metabolite concentrations and half-lives

Blood samples were collected into vaccutainer tubes containing sodium fluoride and potassium oxalate, and frozen immediately. They were shipped in dry ice to the laboratory for analysis, where they were stored frozen and defrosted immediately prior to analysis. The procedure used was a modification of that previously reported.[9] In this modification, the carboxylic acid functional groups (benzoyl ecgonine and ecgonine) were propylated, and the alcohol groups (ecgonine and ecgonine methyl ester) were esterified to the p-fluoro benzoyl ester.

Blood was added to a 20 mL glass culture tube, together with internal standards of ecgonine-D3, benzoylecgonine-D3, cocaine-D3, and ecgonine methanol (1 mL) followed by the addition of acetonitrile (10 mL). The tube was capped and rotated for 5 min, then centrifuged. The supernatant was evaporated to dryness, and reconstituted in a 0.05 mg/mL solution of 18-crown-6-ether in acetonitrile (100 μL). Propyl iodide (50 μL) was added, and the mixture vortexed for 15 s. The tubes were capped and placed into a water bath at 80°C for 1 h. After this the tubes were removed and cooled to room temperature, and a 3M solution of p-fluorobenzoyl chloride in acetonitrile (200 μL) was added, together with triethylamine (100 μL). The tubes were capped and incubated at 60°C for 1 h. After cooling to room temperature, the residue was mixed with saturated borate buffer, pH 9.0 (3 mL), and extracted with n-butyl chloride (1 mL). After mixing for 5 min, the butyl chloride was removed and back extracted with 1M HCl (200 μL). The butyl chloride was aspirated and discarded, and concentrated ammonium hydroxide (100 μL) and saturated solution of ammonium carbonate (100 μL) was added to the acid layer. Following mixing, this solution was extracted with chloroform (50 μL). The chloroform layer was then transferred to an injection vial for analysis by gas chromatography/mass spectrometry (GCMS).

GCMS analysis was performed using a Hewlett Packard 5890 gas chromatograph coupled to a 5970 mass elective detector. The column was a 30 m × 0.25 mm phenylmethylsilicone (econocap, Alltech, Deerfield IL). Separation was achieved using a temperature program from 80 to 295°C at 15/min. The MS was operated in electron impact mode using selected ion monitoring. The ions monitored for each of the derivatized analytes were as follows, with the ions used for quantitation marked (*): cocaine 182*, 82, 303; cocaine-D3 185*, 85, 306; ecgonine methyl ester 82*, 182, 321; ecgonine methyl ester-D3 85*, 185, 324; benzoyl ecgonine 82*, 210, 331; benzoyl ecgonine-D3 85*, 213, 334; ecgonine 82*, 210, 349; ecgonine-D3 85*, 213, 352; norcocaine 302, 210*, 105, 331; and cocaethylene 82*, 196, 317. Each analyte was quantitated with respect to its deuterated analog, except for norcocaine and cocaethylene, which were quantitated with respect to benzoylecgonine-D3 and cocaine-D3 respectively. The method is linear over the range 10–10 000 ng/mL, with within day CV of between 3 and 15%.

Pharmacokinetic modeling for half-life determination of cocaine was performed using Graph Pad v. 2.0. Data points were entered into a database to determine a non-linear regression when the concentration of cocaine was plotted against time for a fit to $y = C_0 * e^{(-kt)}$, where y is the measured value, C_0 is the concentration at time 0, k is the first order elimination constant at t, time (hours). Half-life($T_{1/2}$) is obtained $T_{1/2} = \ln 0.5/k$.

In these two patients there is an obvious delay (Fig. 1) in elimination after 6 h. This slowing is most likely a result of progressive organ failure. Assuming first order decay and fitting all of the data points using either Graph Pad or SPS for Windows v.8.0, half-lives are estimated to be greater than 5 h. The half-life values stated for each patient were determined by eliminating data points beyond 6 h. We do not feel that rigorous multicompartment modeling for so few data points is warranted since it is obvious from the Figure 1 that elimination half-life is not significantly shortened by hyperthermia and, if anything, is delayed.

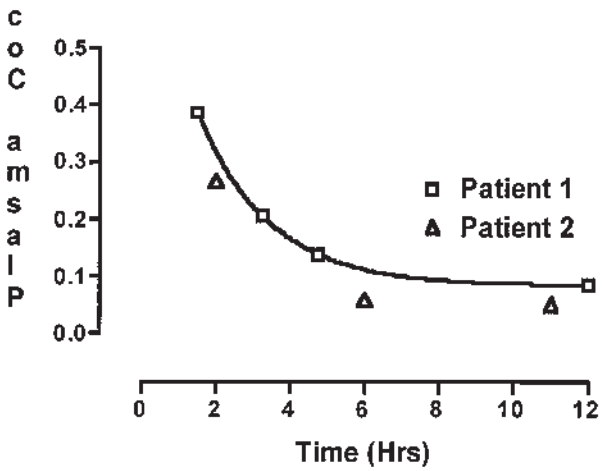

Fig. 1 Plasma cocaine concentrations (mg/L) as a function of time (hours) for patients 1 and 2

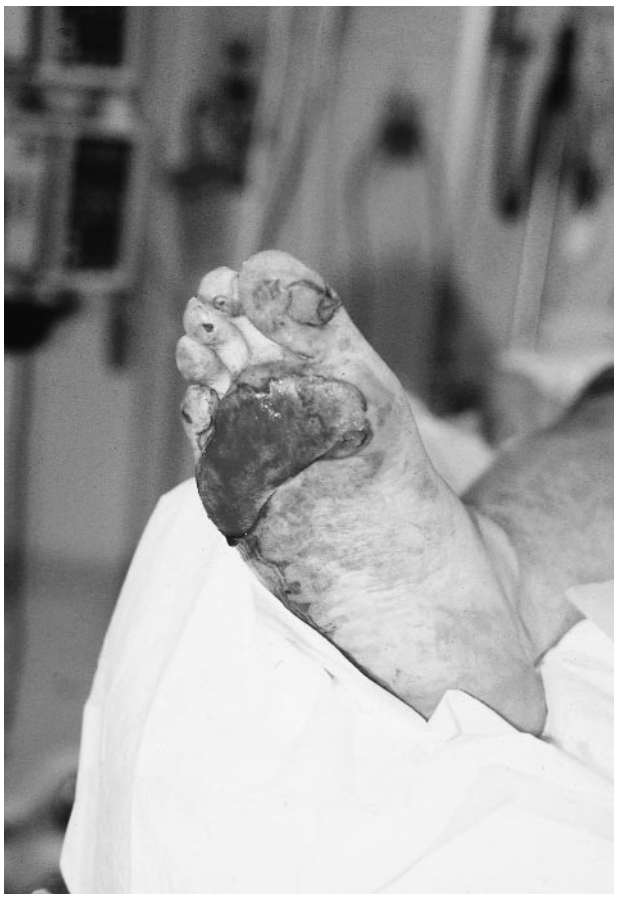

Fig. 2 Excoriations on the feet of patient 1 as a result of self mutilation

PATIENT CASES

Case 1

A 33-year-old obese man was found beating his hands and feet against a storm drain and brought to the emergency department by police. On arrival, he was combative, disoriented, hallucinating, salivating, and profoundly diaphoretic. His core temperature was 42.2°C (108°F). He was also hypotensive and tachycardiac (58/40 mmHg and 161 bpm). Multiple IV puncture sites were noted, as well as deep scratches and excoriations over the extremities (Fig. 2). His family reported that he had been hospitalized on at least three occasions previously for cocaine toxicity, and that he had used cocaine approximately 1 h prior to his admission.

In spite of intensive resuscitative and cooling measures, he followed a relentlessly downhill course, with onset of both rhabdomyolysis, disseminated intravascular coagulation and multisystem organ failure. With aggressive measures his temperature was transiently lowered to 38.3°C (101°F), but then increased back to 40.2°C (105°F). His creatine phosphokinase (CPK), which had been 6200 IU on arrival increased to 19 245 IU after 8 h. At the same time, his creatinine rose from 3.5 to 6.3 mg/L. An admission ECG demonstrated conduction delays, ventricular hypertrophy, and early repolarization. He began to bleed profusely from all the intravenous puncture sites and from all mucosal surfaces 10 h after admission. He became asystolic 2 h later and resuscitative attempts were unsuccessful.

Significant findings at autopsy are listed in Table 1. Cocaine was not detected in postmortem blood. Using the time of injection 1 hour before arrival at the emergency department, then the decedent would have had a peak concentration of 0.61 mg/L at the time of administration. The half life of cocaine was 122 min.

Table 1 Significant postmortem findings for Case 1

Left ventricular hypertrophy (1.8 cm)
Myocyte variation in size with scattered hypertrophic nuclei
Myocardial contraction bands
Coronary atheromas with insignificant occlusion
Brain with global edema, blunting of gyri and narrowing of sulci
Pulmonary congestion
Passive congestion of liver
Bilateral abrasions of anterior knees and feet
Renal vascular changes consistent with hypertension

Case 2

A 22-year-old obese man was found lying on the street, clawing at the pavement. On arrival in the emergency department, his presentation was similar to Case 1, except that his temperature was 39.9°C (104.6°F), and he was hypertensive. His family reported two previous admissions for cocaine toxicity. Vital signs on arrival included a heart rate of 176 bpm, a blood pressure of 250/140 mmHg, and a

Table 2 Cocaine and metabolite concentrations (mg/L) from patient 1.

Time (hours) admin	Time (hours) present	Temp °C	COC	EME	CE	E	NC	BE
1.5		41.5	0.387	0.953	0	0.612	0.052	4.7
3.25		39.7	0.207	1.207	0	0.667	0.026	5.8
4.75		40.1	0.137	0.717	0	0.675	0.018	4.6
12		39.6	0.086	0.587	0	0.878	0.011	4.2

Admin: time after administration; Present: time after presentation; COC: cocaine concentrations; EME: ecgonine methyl ester; CE: cocaethylene; E: ecgonine; NC: norcocaine; BE: benzoylecgonine

Table 3 Cocaine and metabolite concentrations (mg/L) from patient 2

Time (hours) admin	Time (hours) present	Temp °C	COC	EME	CE	E	NC	BE
	2	40.3	0.266	0.173	0	0.155	0	0.9
	6	37.5	0.059	0.077	0	0.234	0	1.1
	11	37.7	0.052	0.048	0	0.23	0	0.8

Admin: time after administration; Present: time after presentation; COC: cocaine concentrations; EME: ecgonine methyl ester; CE: cocaethylene; E: ecgonine; NC: norcocaine; BE: benzoylecgonine

respiratory rate of 48. Over the course of 72 h, he developed rhabdomyolysis and renal failure with laboratory evidence of disseminated intravascular coagulopathy, but no overt bleeding. An initial CPK of 1937 IU rose to 85 000 IU after 24 h. His ECG showed nonspecific intraventricular conduction delay, early repolarization, ST-T wave abnormalities, and inferior wall ischemia. An ECHO cardiogram showed mild left ventricular hypertrophy, a mild decrease in left ventricular systolic function, mild enlargement of the aortic root, and mild mitralvalve prolapse. He survived with supportive care and was discharged after a 6-day hospital stay. He admitted to smoking crack cocaine as part of a birthday celebration the night of admission. Pharmacokinetic modeling based on showed a cocaine half-life of 114 min.

DISCUSSION

As the number of chronic stimulant abusers has increased, so also have the number of reported cases of excited delirium (ED). Compared to cocaine users who die from heart disease, or even massive overdose (bodypackers), patients with ED are more frequently black, male, and younger when they die. They are also more likely to develop hyperthermia, die in hot weather, and in police custody,[8] and to be obese.

Studies have shown that the body mass index (BMI) of trauma victims who use cocaine prior to death is higher than the BMI of decedents where cocaine is the actual cause of death.[1] At the same time, other studies have shown that the BMI of cocaine-using ED victims is higher than that of other cocaine-related deaths.[8] Whether the increased fat content of these individuals has any bearing on the way in which they store or metabolize cocaine, or on cocaine's apparent volume of distribution, is not known. It is known, however, that cocaine and benzoylecgonine concentrations in autopsy blood from ED decedents overlap concentrations seen in other, non-ED, cocaine-related deaths,[8] just as concentrations in non-ED death overlap concentrations in cases where the presence of cocaine is only an incidental finding.[1] To further complicate the issue, cocaine and benzoylecgonine concentrations in cocaine deaths and where cocaine is an incidental finding overlap concentrations found in drug abusers presenting to an emergency department.[10]

The etiology of the behavior and temperature control abnormalities in ED victims has been well characterized. Compared to other cocaine-related deaths, the number of D2 receptors in the temperature regulatory centers of the hypothalamus is decreased in those patients who die from ED.[11,12] With fewer D2 receptors, D1-mediated temperature increases are unopposed, perhaps explaining why decedents are invariably hyperthermic. There have been limited studies that have shown that even limited exposure to cocaine can alter dopamine receptor concentration.[13] Alterations in the number and distribution of κ2 receptors within the amygdala appear to explain the distinctive psychotic symptoms and violent agitation.[12]

The two cases described here exhibited the classic findings of excited delirium. Interestingly, the

measured half-life for cocaine and the blood concentrations observed in these two individuals were consistent with values reported from normothermic, healthy, human volunteers (0.1–0.6 mg/L).[14–20] If anything, the half-lives of 132 and 114 min in these patients were prolonged. This suggests that, at least in the living, cocaine metabolism is not accelerated by elevated body temperature, even in the presence of profound hyperthermia as in Case 1. These observations are difficult to reconcile with the findings of an in-vitro study by Walker et al.,[21] who observed that when cocaine-spiked blood samples from healthy, non-drug using, volunteers, were stored at 40°C, measured concentrations decreased from 1000 ng/mL to 20 ng/mL over a 6 h period.

Although we have no data that would address the issue one way or another, one possible explanation for this disparity is that the route for cocaine metabolism may be different in-vitro. There are, however, many confounding variables that could have affected the disposition of drugs in both of these cases; hyperthermia, renal failure, multisystems organ failure and the use of other medications all could have altered the clearance of cocaine.

Concentrations of the other cocaine metabolites are very difficult to interpret, although the detection of norcocaine is of some interest. It had originally been thought that oxidative metabolism of cocaine did not occur in humans. It is becoming increasingly clear, however, that small amounts of norcocaine are formed in chronic users, particularly those who consume alcohol.[22] Norcocaine formation is thought to be responsible for the hepatic damage observed in animals,[23,24] and may yet prove to have a role in human disease.

Clinical and experimental data suggests that cocaine is sequestered in deep body stores and that benzoylecgonine accumulates in chronic users.[25,26] The same is very likely true for the other metabolites, but the issue has never been thoroughly studied. The initial benzoylecgonine concentration was not known in either case, and renal failure supervened in both. Unlike cocaine, which is metabolized mainly to ecgonine methylester and benzoylecgonine, the metabolites are largely excreted in the urine. Abnormal renal function in both individuals rules out any speculation about the effect of temperature on the half-life of the metabolites.

In spite of the limitation imposed by clinical considerations, these two cases do provide further evidence that catastrophic cocaine reactions, such as those described here, are not related to dose, concentration, route of administration or delayed cocaine clearance. At best, these types of reactions appear to be idiopathic and predictable only from a previous history of such reactions. Cocaine and metabolite concentrations, whether measured in the living or the dead, must be interpreted with great caution.

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