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Fatal Excited Delirium Following Cocaine Use: Epidemiologic Findings Provide New Evidence for Mechanisms of Cocaine Toxicity

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ABSTRACT: We describe an outbreak of deaths from cocaine-induced excited delirium (EDDs) in Dade County, Florida between 1979 and 1990. From a registry of all cocaine-related deaths in Dade County, Florida, from 1969–1990, 58 EDDs were compared with 125 victims of accidental cocaine overdose without excited delirium. Compared with controls, EDDs were more frequently black, male, and younger. They were less likely to have a low body mass index, and more likely to have died in police custody, to have received medical treatment immediately before death, to have survived for a longer period, to have developed hyperthermia, and to have died in summer months. EDDs had concentrations of cocaine and benzoylecgonine in autopsy blood that were similar to those for controls. The epidemiologic findings are most consistent with the hypothesis that chronic cocaine use disrupts dopaminergic function and, when coupled with recent cocaine use, may precipitate agitation, delirium, aberrant thermoregulation, rhabdomyolysis, and sudden death.

KEYWORDS: forensic science, cocaine, crack, excited delirium, neuroleptic malignant syndrome, rhabdomyolysis, epidemiology

Wetli and Fishbain (1) first described the syndrome of fatal excited delirium (ED) in seven users of cocaine hydrochloride who died between April 1983 and May 1984. Victims of fatal ED exhibited the acute onset of bizarre and violent behavior, which was characterized by one or more of the following: aggression, combativeness, hyperactivity, extreme paranoia, demonstration of unexpected strength, or incoherent shouting. The incident was followed by fatal cardiorespiratory arrest. Four of the seven developed hyperthermia before death. When this case series was first reported, it was not clear whether ED was caused by an undetected contaminant in cocaine preparations, by another drug that was not detected by usual toxicologic methods, by techniques used by police to restrain victims, or whether it was a newly recognized outcome of cocaine use. Over the years since the first report, others have appeared (2–5). Furthermore, reports of rhabdomyolysis associated with cocaine use have also noted that excitement, delirium, and hyperthermia preceded the onset of this condition (6–14).

There is now confusion in the medical literature about whether extreme agitation, delirium, hyperthermia, and rhabdomyolysis are effects of cocaine that occur independently and at random among cocaine users, or whether these features are linked by common toxicologic and pathologic processes. It is also not clear how frequently ED and hyperthermia are noted in victims of accidental cocaine toxicity (10,15).

We report here data from a population-based registry of all cocaine related deaths in Dade County, Florida and the results of a case-control analysis based on these data for 1979–1990—the period over which the first reported cases of ED occurred in the United States. With these data and analyses, we identify risk factors for fatal ED and discuss possible mechanisms for fatal ED.

Methods

Medical Examiner Investigations

In Dade County, the Metropolitan Dade County Medical Examiner Department (MDCMED) routinely investigates all sudden and unexpected natural deaths as well as unnatural deaths suspected to have resulted from suicide, homicide, accidental injury, the untoward effects of drugs, or overdose from drugs. Such deaths are investigated even if they occur after a period of hospitalization.

Each investigation of the deaths reported here included a description of the scene and circumstances surrounding the death, a review of records from emergency departments, and a complete autopsy with toxicologic analysis (16–18). Postmortem blood was preserved in sodium fluoride and refrigerated to retard further metabolism, hydrolysis, and decomposition of drugs. Urine was refrigerated and screened for the presence of common drugs of abuse and their metabolites with gas chromatography (GC) or gas chromatography/mass spectrometry (GC/MS) (19). If the urine drug screen was positive for cocaine metabolites, then blood cocaine concentrations were measured by GC/MS (20). Beginning in 1988, for some decedents who had cocaine metabolites detected in urine, blood concentrations of benzoylecgonine (a cocaine

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metabolite) were measured by fluorescence polarization immunoassay (Abbott TDX™) or by GC/MS. By 1990, benzoylecgonine was quantified for all such decedents.

Epidemiologic Analysis

Records of the MDCMED were reviewed to identify accidental deaths due primarily to the toxic effects of cocaine and not to trauma, violent injury, the toxic effects of another drug, or to another known cause. This classification excludes persons with concentrations of cocaine in postmortem blood who were homicide, trauma, or suicide victims, body packers (persons who smuggled cocaine into the United States by swallowing packets of the drug) (21), drowning victims, and decedents with toxicologic evidence of heroin use.

Victims of fatal excited delirium (EDDs) are defined as those who experienced accidental cocaine toxicity and exhibited an episode of bizarre and violent behavior (as described above) which was followed by sudden death. The comparison group (termed other accidental cocaine toxicity deaths or OACTDs) comprises victims of accidental cocaine toxicity who, according to witnesses, did not exhibit features of ED and who died during or after 1979—the year in which the first EDD was identified in Dade County.

Demographic data, autopsy pathology findings, and results of toxicology tests were abstracted from reports of the medicolegal investigations. The route by which cocaine was administered was determined by reviewing descriptions of the scene provided by forensic investigators and witnesses and from drugs and drug paraphernalia found at the scene of death.

Because the concentration of cocaine in autopsy blood may be reduced by premortem metabolism, leaching, and deterioration (22), scene reports were used to estimate survival time from the onset of overdose to death in order to adjust for these effects. For blood cocaine concentrations that were below detection limits, values of one half the detection limits were assigned for statistical analyses. The possibility that adiposity is a risk for death from ED was assessed with the body mass index (BMI) (23), which was computed as the body weight in kilograms divided by the square of the height in meters.

Statistical analyses were performed with statistical analysis system software for the personal computer (24,25). The Shapiro-Wilk test was used to determine whether data were normally distributed. Differences between normally distributed groups were tested for significance with the student's *t*-test. For variables not normally distributed, results from both the student's *t*-test and the Wilcoxon rank sum tests were computed. The Chi-square test was used to test the statistical significance of differences between EDDs and OACTDs for categorical variables. If the expected cell frequency of a contingency table was fewer than five, the Fisher's exact method was used.

Confounding and interaction between variables were assessed with logistic regression models (26,27). Because there were only four female EDDs, the logistic regression models were restricted to males. The final model was selected to maximize the log likelihood statistic and to include variables that persisted as independent significant risk factors.

Results

After the first report in 1979, the frequency of EDDs increased in a pattern similar to that of all other deaths attributed to the acute toxicity of cocaine (Fig. 1). For the period from 1979 to 1990, EDDs accounted for 16.5% of all accidental cocaine toxicity deaths. Although the first EDDs were white, beginning in 1985, the ratio of EDDs to all other deaths from accidental cocaine toxicity (termed ACTDs in Figs. 1 and 2) increased for blacks, but remained stable or declined for whites (Fig. 1). Compared with ACTDs, the range of ages for EDDs was smaller and more stable over the study period (Fig. 2).

Compared with OACTDs (the ACTDs that were witnessed and showed no signs of ED), EDDs were more likely to be black and male (Table 1). Male EDDs were also significantly younger than male OACTDs (Table 1). Although measures of central tendency for height, weight (data not shown), and BMI were similar for EDDs and OACTDs, there were comparatively few male EDDs with BMIs in the lowest quartile (Table 1).

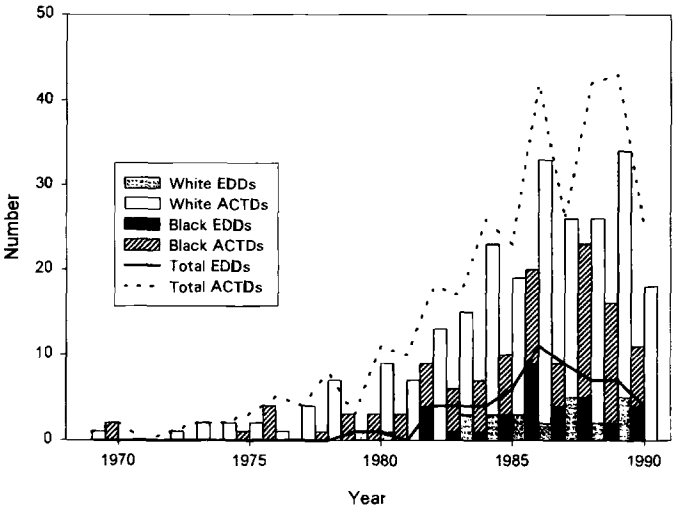

FIG. 1—*Deaths from excited delirium (EDDs) and from accidental cocaine toxicity without ED, stratified by race, Dade County, Florida, 1969–1990. Deaths with no information about behavior during the overdose period are included in the accidental cocaine toxicity death (ACTD) category; deaths attributed to the combined effects of heroin and cocaine, to cocaine toxicity and drowning or to cocaine-induced suicide are excluded.*

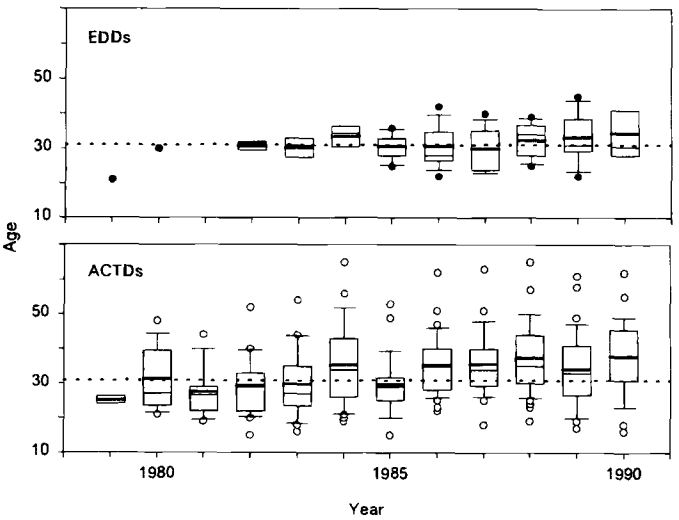

FIG. 2—*Distribution of age by year for EDDs and ACTDs, 1979–1990. Boxes specify 25th and 75th percentiles and bars connected by vertical lines specify 10th and 90th percentiles; thin horizontal bars inside boxes specify medians and thick horizontal bars, means; data points outside the 10th and 90th percentiles are plotted. See Fig. 1 for definition of ACTDs. The broken lines extending across the plots represent the mean for all EDDs.*

TABLE 1—*Demographic and physical characteristics for excited delirium and other accidental cocaine toxicity deaths.*

Characteristic	Excited Delirium Deaths (N = 58)		Other Accidental Cocaine Toxicity Deaths* (N = 125)		P
	N	%	*N*	%	
Males					
White	23	43	53	72	<0.01†
Black	31	57	21	28	
Females					
White	2	50	35	69	0.59‡
Black	2	50	16	31	
Age (years)	*Mean*	*N*	*Mean*	*N*	
Males	31.3	54	36.3	74	<0.01§
Females	32.5	4	31.6	51	0.83§
Body Mass Index‖					
Males	27.9	54	27.0	72	0.36§
Females	24.5	4	23.9	51	0.82§
Male Body Mass Index Quartile¶	*N*	%	*N*	%	
17.1–23.2	8	15	23	32	
23.3–25.7	17	31	15	21	0.15†
25.8–30.9	15	28	17	24	
31.0–50.4	14	26	17	24	
Unknown	0		2		

*See text for definition; excluded from the OACTD classification were: Deaths attributed to the combined effects of heroin and cocaine, cocaine toxicity and drowning, or cocaine-induced suicides: deaths before 1979 (the year of the first EDD), and deaths with no information about behavior during the overdose period

†Chi-square test.

‡Fisher's exact test.

§Student's t-test; similar P values were obtained with the Wilcoxon rank sum test.

‖Weight in kg/height in m^2.

¶Quartiles of body mass index are defined by the distribution for male EDDs and other OACTDs combined; the unknown category was eliminated for calculation of percentages and the chi-square statistic.

TABLE 2—*Description of circumstances of death for excited delirium and other accidental cocaine toxicity deaths.*

Characteristic	Excited Delirium Deaths (N = 58)		Other Accidental Cocaine Toxicity Deaths* (N = 125)		P
	N	%	*N*	%	
Route of Cocaine Administration†					
Injection	9	41	10	17	
Intranasal	7	32	33	57	0.09‡
Smoking§	5	23	11	19	
Other	1	5	4	7	
Unknown	36		67		
Died in Police Custody					
No	36	62	122	98	<0.01‖
Yes	22	38	3	2	
Medical Treatment					
None	7	12	48	38	<0.01‖
Some	51	88	77	62	
Seizures†					
Absent	37	73	59	56	0.04‖
Present	14	27	47	44	
Unknown	7		19		
Hyperthermia†					
Absent	1	3	9¶	35	<0.01‖
Present	38	97	17¶	65	
Unknown	19		99¶		
Season					
June–September	32	55	41	33	<0.01‖
Rest of year	26	45	84	67	
Survival Time†					
<1 h	19	36	54	57	
1 to 6 h	14	26	15	16	<0.01‡
7 to 12 h	9	17	3	3	
>12 h	11	21	22	23	
Found dead or unknown	5		31		

*See text for definition.

†Unknown category eliminated for calculation of percentages and P value.

‡Fisher's exact test.

§Crack or free base cocaine; two EDDs and one OACTD smoked free base and the rest smoked crack.

‖Chi-square test.

¶These estimates are inaccurate; see text for explanation.

The route of cocaine administration could not be determined for 64% of EDDs and 54% of OACTDs. For the subjects with an identified route of administration, the most frequent was injection for EDDs and inhalation for OACTDs (Table 2). The frequency of smoking crack or user-prepared cocaine free base was similar for the two groups. EDDs received emergency medical treatment and died while in police custody more commonly than OACTDs.

Seizures were less frequently observed in EDDs than in OACTDs. For decedents with records of pre-morbid body temperature, hyperthermia was noted in 97% of EDDs and in 65% of OACTDs. Many victims had rectal temperatures over 40°C (104°F) at death. Because body temperature was measured and recorded if it was suspected to be above normal, it is likely that most OACTDs with unknown temperatures were normothermic. Deaths from ED occurred more often in the summer (June–September) than in any other season. In an unadjusted comparison, this distribution is significantly different from the distribution of OACTDs (Table 2).

For blood cocaine concentrations in both survival categories, the median, 25th and 10th percentiles were similar for EDDs and OACTDs (Fig. 3); compared with OACTDs, the upper 75th and 90th percentiles for EDDs were lower. In 1988, benzoylecgonine was not quantified in 28% of all subjects; in 1989, 13% were not tested, and in 1990, all subjects were tested. There was no difference between EDDs and OACTDs with regard to the frequency with which benzoylecgonine was quantified (P = 1.00, Fisher's exact test). The median and 10th percentiles for blood benzoylecgonine concentrations were similar across survival categories for EDDs and OACTDs, but the 25th percentile was higher for EDDs than for OACTDs in both survival categories. A scatter plot of $\log_{10}$- transformed concentrations of blood cocaine and benzoylecgonine (Figs. 4 and 5) shows no evidence of a unique relation between these variables for EDDS; there are, however, fewer EDDs with blood benzoylecgonine concentrations lower than 1 mg/L.

The concentrations of ethanol in blood were similar (P = 0.24, student's t test; P = 0.79, Wilcoxon rank sum test) for EDDs (mean = 0.008%, median = 0.000%), and OACTDS (mean = 0.014%, median = 0.000%). Most other drugs identified in urine were detected in fewer than 5% of subjects in either group and there were no statistically significant differences between EDDs and OACTDs for any of these drugs ($P > 0.05$, Chi-square test).

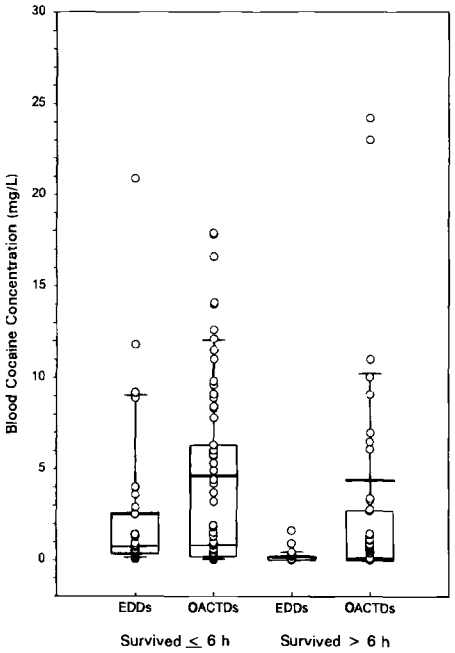

FIG. 3—*Blood cocaine concentrations by survival time for EDDs and OACTDs; see Fig. 2 for description of box plots; all data points are plotted except for two outliers (45.3 and 68.3 mg/L) in the OACTD group that survived >6 h.*

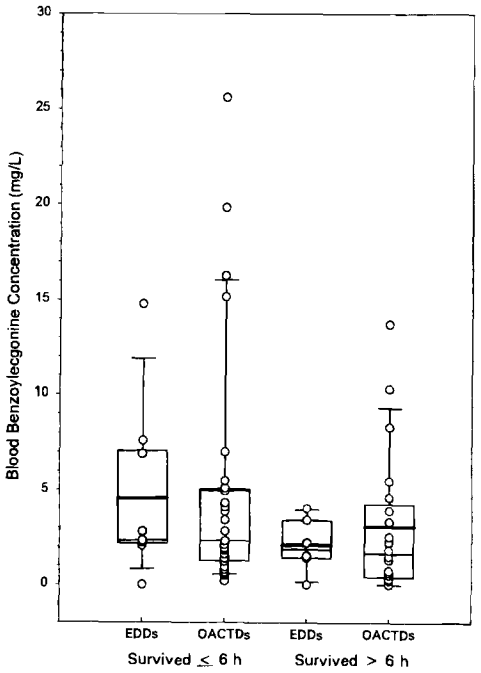

FIG. 4—*Blood benzoylecgonine concentrations by survival time for EDDs and OACTDs; see Fig. 2 for description of box plots; all data points are plotted.*

The two groups were similar with regard to mean heart weight (407 g for EDDs and 399 g for OACTDs, $P = 0.62$, student's t-test), gross evidence of left ventricular hypertrophy (16% for EDDs and 23% for OACTDs, $P = 0.26$, Chi-square test) and gross evidence of past myocardial infarction (2% for EDDs and 6% for OACTDs, $P = 0.23$, Chi-square test). Gross evidence of brain abnormalities (tonsilar herniation, ventricular compression, intracranial bleeding, leptomeningeal hemorrhage, and cerebrovascular

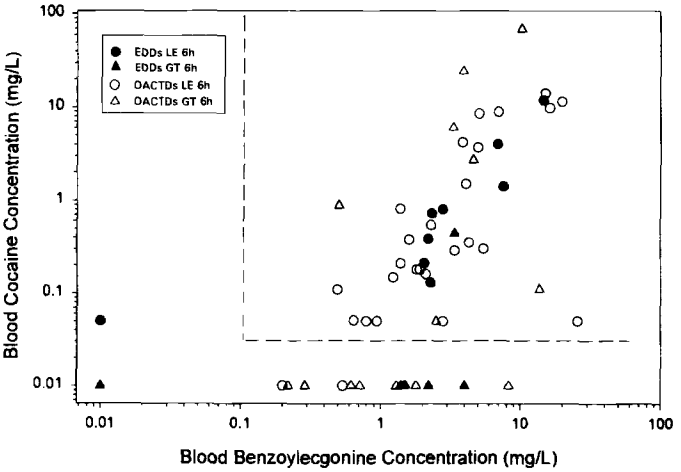

FIG. 5—*Blood cocaine concentrations by blood benzoylecgonine concentrations for EDDs and OACTDs who had measurements for both. All concentrations were log 10-transformed; zero concentrations were converted to 0.01 mg/L in order to display them, and are outside the dashed axes.*

atherosclerosis) was detected in 10% or fewer of the decedents in both groups, and EDDs were similar to OACTDs for every comparison ($P > 0.20$, Fisher's exact test).

The independent risk factors identified with the logistic regression model are a BMI in the upper three quartiles (based on the distribution for male EDDs and OACTDs combined), black race, and young age (Table 3). When each of the upper three quartiles of the BMI were compared separately with the lowest, each showed

TABLE 3—*Crude and adjusted odds ratios for important risk factors for fatal excited delirium among males.*

	Crude Analysis		Adjusted Analysis*	
Risk Factor	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
BMI Quartiles 2–4†	2.7	1.1–6.6	4.2	1.5–11.2
Black Race	3.5	1.7–7.4	3.3	1.5–7.5
Younger Age‡	1.1	1.0–1.1	1.1	1.0–1.1
Death in Police Custody	22.3	4.9–100.7		NA*
Hyperthermia	12.1	6.8–52.8		NA*
Male Gender	9.3	3.2–27.3		NA*
Smoking or Injection vs. Other Route	3.1	1.1–8.6		NA*
Summer Season	2.5	1.3–4.8		NA§

*Results were obtained using logistic regression with ED status as the outcome (for EDDs, $N = 54$; for OACTDs, $N = 72$). In adjusted analyses, hyperthermia was excluded because body temperature before death was recorded in only 67% of EDDs and 21% of OACTDs; death in police custody and female gender were excluded because only 2% of the OACTDs died in police custody and only 7% of EDDs were female, resulting in a large odds ratios with wide confidence intervals; route of cocaine administration was excluded because it was unknown for 62% of EDDs and 54% of OACTDs.

†BMI (body mass index) = weight (kg)/height (m)^2; referent category = <23.3 kg/m^2; the odds ratios for BMI as a continuous variable were nonlinear; it was converted to two categorical variables determined by the gender-specific distribution of subjects in the ED and OACTD groups combined.

‡Modeled as a continuous variable with older age as the reference.

§Not statistically significant ($P > 0.05$) in the logistic regression model.

a similar elevated risk in both crude and adjusted analyses, suggesting a threshold rather than a dose-response relation. Although age was best modeled as a continuous variable, we found that the odds ratio (OR) for age was maximum (OR = 9.3, 95% CI = 2.5, 34.6) when it was transformed into a dichotomous variable comparing the lower three quartiles for all subjects (<39 years) with the upper quartile. Summer season was of borderline significance in logistic regression models with other significant risk factors. The crude and adjusted ORs for these risk factors are summarized in Table 3.

Discussion

If ED is caused by an acute, high dose of cocaine, then EDDs would have cocaine concentrations and ratios between cocaine and benzoylecgonine concentrations in postmortem blood that are higher than OACTDs, as the elimination half-life of benzoylecgonine from plasma is more than three times longer than cocaine (4.5 versus 0.5–1.5 h). The data in Figs. 3 and 5 do not support this hypothesis. If ED is caused by a drug other than cocaine, then we should have detected it more frequently in EDDs than in OACTDs. Although cocaethylene concentrations were not measured for any subjects in this study, the fact that blood concentrations of both cocaine and ethanol were similar for EDDs and OACTDs suggests this drug does not cause ED.

Kosten and Kleber (30) hypothesized that the onset of ED is initiated by a relative decrease in concentrations of intrasynaptic dopamine in the hours following a period of repeated (binge) cocaine use. If this hypothesis were to explain why EDDs were different from OACTDs, then a scatter plot of blood cocaine and benzoylecgonine concentrations would show a unique clustering of EDDs with low concentrations of blood cocaine and high concentrations of blood benzoylecgonine. Although a few EDDs who survived 6 h or longer had low blood cocaine/benzoylecgonine ratios (Fig. 5), there are many other EDDs with much higher ratios. There are also many OACTDs with ratios similar to those for EDDs, suggesting this pattern is not unique to the ED syndrome. Furthermore, preliminary studies have failed to detect a decrease in brain dopamine concentrations in EDDs as compared with OACTDs (Mash DC, 1995, unpublished data).

For EDDs who survived for fewer than 6 h, as well as for many OACTDs, those with low benzoylecgonine concentrations had low blood cocaine concentrations, and those with high benzoylecgonine concentrations had high blood cocaine concentrations (Fig. 5). It appears, therefore, that the high benzoylecgonine concentrations in both EDDs and OACTDs are not due to the metabolism of single high doses of cocaine and that binge use preceded death in both EDDs and OACTDs. Although most EDDs had been using cocaine frequently enough to have concentrations of benzoylecgonine greater than 1 mg/L, many OACTDs had not used cocaine long enough or intensively enough to achieve this concentration, suggesting that EDDs had binged for longer periods than OACTDs.

Compared with OACTDs, EDDs were more likely to be black, male, and younger. We suspect these demographic risk factors are confounded by the comparatively high prevalence of chronic cocaine use among persons with these characteristics. Although detailed data for drug use patterns among cocaine users have not been published and are not in the records of the MDCMED, chronic cocaine use can be inferred from the route of cocaine administration. Persons who smoke crack or user-prepared cocaine free base or who inject cocaine hydrochloride are more likely to binge on a chronic basis than those who administer cocaine hydrochloride by nasal insufflation (31,32).

Epidemiologic data from other studies suggest that crack use among blacks is more prevalent than among other races (33–38)—even though this difference is related to socioeconomic and cultural factors rather than to race itself (39). The epidemic of crack use that began in United States in 1985 has been characterized by aggressive marketing strategies in black communities (40,41). This time period coincides with the increase in EDDs among blacks in Dade County (Fig. 1).

Of subjects with an identified route of administration, 5 of 12 black EDDs smoked crack or cocaine free base before developing ED, as compared with none of 10 white ED victims. The first ED death in a black person that was attributed to crack or free base smoking occurred in 1986. Before then, injection was the only route of administration identified for black EDDs. Compared with those who died after administering cocaine by other routes, subjects who died after injecting or smoking cocaine were 7.7 times (95% CI 2.9–20.2) more likely to be black.

Because there were only a few female EDDs, confounding between gender and other risk factors could not be assessed directly. Because males are about twice as likely as females to smoke crack (39), the sizable risk for males is likely to be confounded by route of administration and, as hypothesized, by chronic use. We also suspect there is a gender-specific risk for hyperactivity in response to the onset of the ED syndrome—similar to the male risk for violence and aggression that appears in most societies. Such activity would increase the risk for hyperthermia—a major risk for death in those who develop ED. Male gender may also be confounded by the risk for hyperthermia in persons with BMIs in the upper three quartiles.

The age range for EDDs has been identified as a substantial risk factor for crack smoking. Persons aged 20–34 years are about twice as likely to use crack as those aged 15–19 years and more than six times as likely as those 35 years or older (39). The time at which the age distributions for OACTDs and EDDs began to differ substantially (Fig. 2) corresponds with the onset of the crack epidemic in Dade County.

There are many similarities between ED and the neuroleptic malignant syndrome (NMS): Both are characterized by delirium, agitation, increased psychomotor activity, and hyperthermia. Because NMS follows the administration of drugs that block dopamine receptors (30,42,43), it has been hypothesized that a period of intense cocaine use might reduce levels of intrasynaptic dopamine at certain locations in the brain, thereby producing a similar effect.

The toxicologic and epidemiologic data in this study suggest that a pattern of cocaine use characterized by repeated binges is associated with the development of fatal ED. It is not clear, however, how frequently one must binge in order to be at increased risk. There is now evidence that chronic cocaine use produces adaptive changes involving dopamine receptors. Both the density and sensitivity of D1 and D2 receptor subtypes are altered by drugs that increase intrasynaptic dopamine (44). Chronic cocaine use decreases the density of receptors of the D1 subtype throughout the striatal reward centers, but does not affect the number of D2 receptors. Compared with drug-free controls, the number of cocaine recognition sites on the striatal dopamine transporter is increased in cocaine users without evidence of ED (45). No such increase is seen in victims of ED (46), suggesting that they may have problems clearing dopamine from their synapses—a condition

that could lead to agitation and delirium. ED appears to be generated not by decreased levels of intrasynaptic dopamine, but by increased intrasynaptic concentrations resulting from a defect in the regulation of the dopamine transporter.

Hyperthermia conveys a high risk for fatal ED and discussions with emergency medicine specialists suggest that aggressive efforts to lower body temperature are effective in preventing death in victims of ED. By definition, victims of ED were hyperactive and therefore capable of generating body heat through skeletal muscle activity. Because BMI is correlated with both muscle mass and body fat, the risk associated with a BMI above 23.2 suggests there may be a threshold for an effect on body temperature by either muscle mass, body fat, or both. Temporal clustering of EDDs in summer months suggests that ambient temperature and perhaps humidity may also affect the evolution of hyperthermia. A similar association has been suggested between summer heat and humidity and hyperpyrexia in patients treated with phenothiazines and other antipsychotic drugs that block dopamine receptors (47,48).

Kosten and Kleber (30) hypothesized that the hyperthermia associated with ED results from extensive muscular activity in a warm environment coupled with aberrant thermoregulation in the hypothalamus and mesolimbic system. In victims of ED, the number of D2 receptors is substantially reduced in the temperature regulatory centers of the hypothalamus (46). Because D2 receptors are involved in processes that decrease core body temperature, a decrease in number would lead to unopposed increases in temperature that are mediated by the D1 receptors which are not affected in victims of ED (49).

Compared with OACTDs, EDDs were much more likely to have died in police custody, and force was usually required to restrain them. Descriptions of the events that preceded death indicate that all victims showed clear evidence of ED before encountering a law enforcement officer. Therefore, events that occurred in police custody are not involved in the onset of ED. Every death that occurred in police custody was thoroughly investigated for evidence of life-threatening trauma; no such evidence was found in police reports or during postmortem examination.

Positional asphyxia and a restraint-induced increase in endogenous catecholamines have been hypothesized as causes of EDD (4,5). Because many EDDs were not in police custody, these are not necessary components of a mechanism for death. It is possible, however, that victims of ED may be more sensitive than other cocaine users to the life-threatening effects of a catecholamine surge. This mechanism is consistent with the descriptions of many EDDs in which a sudden cardiorespiratory arrest occurred after the victims had been handcuffed following periods of struggle. Although it has been hypothesized that underlying myocardial disease could contribute to the risk for death in EDDs from high levels of catecholamines (49), heart weight, ventricular hypertrophy, and past myocardial infarction are not risk factors for fatal ED.

Since 1987, there have been more than 20 case reports of cocaine-associated rhabdomyolysis (CAR) in the medical literature. Many note features of hyperactivity, delirium, and hyperthermia that are identical to those of ED. We agree with others (50) that ED and CAR have many features in common, and may be caused by the same mechanism(s).

The evidence in support of our conclusion is: 1) rhabdomyolysis was first noted in Dade County cocaine users in 1982—three years after the first EDD; 2) the pattern of occurrence of cocaine-associated rhabdomyolysis in Dade County reported by Roth et al. (9) matches our epidemic curve for EDD; 3) both ED and cocaine-associated rhabdomyolysis are considered to be newly recognized effects of cocaine; 4) many persons with cocaine-associated rhabdomyolysis also exhibit the classic features of ED, hyperthermia, or both; and 5) both skeletal muscle activity and hyperthermia, which are prominent features of ED, are known causes of rhabdomyolysis.

Some have suggested that the severity of CAR is related to the severity of cocaine intoxication (50,51). If CAR is caused by the same mechanism as ED, then, according to our data, chronic rather than acute cocaine use is responsible. This conclusion is supported by many case reports for CAR describing patterns of chronic cocaine use that preceded the onset of rhabdomyolysis (6,11–13,50,52–54). Support for the hypothesis that chronic cocaine use causes CAR also comes from reports of muscle enzyme elevations in asymptomatic chronic cocaine users (55–56) and in untreated schizophrenics (57), supporting the hypothesis that chronic alterations in dopaminergic function can affect skeletal muscle physiology.

Some reported cases of CAR had no evidence of ED (6,11,13,54,59), and some had no evidence of hyperthermia (11,13,14,52,53,60). These data suggest that if ED and CAR are caused by the same mechanism, there is a spectrum of severity that ranges from rhabdomyolysis with no ED or hyperthermia to various combinations of these three conditions. We conclude that ED, CAR, and NMS have many common features that can be explained by aberrant dopaminergic function. The evidence we present also suggests that chronic administration of cocaine is responsible for persistent changes in dopaminergic function that place cocaine users at risk for ED and are likely to be the cause of CAR.

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