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Relating Cocaine Blood Concentrations to Toxicity—an Autopsy Study of 99 Cases

REFERENCE: Karch SB, Stephens B, Ho C-H. Relating cocaine blood concentrations to toxicity—an autopsy study of 99 cases. J Forensic Sci 1998;43(1):41–45.

ABSTRACT: We conducted a retrospective study of 48 men with cocaine-related deaths (CTOX), and a control group of 51 male cocaine users who died of lethal trauma (TRAU). Regression analysis and multiple t-tests were used to assess the relationship between cocaine and benzoylecgonine concentrations as well as autopsy measurements. Findings: Mean age was similar (35.9 vs 34.8 years, $p = .549$). Cocaine blood concentrations were not significantly different (1.12 vs .487 mg/L, $p = .10$), but mean BE concentrations were higher in CTOX (1.54 vs .946 mg/L, $p = .018$). CTOX decedents had a lower Body Mass Index (BMI) (24.6 vs 30.6, $p = <.0001$), larger hearts (426 vs 369, $p = .009$), and heavier lungs, livers, and spleens (1275 g vs 1007 g, $p = .009$, 1896 g vs 1628 g, $p = .008$, 193 g vs 146 g, $p = .001$). Conclusions: (1) Blood cocaine concentrations in cocaine-related deaths are indistinguishable from postmortem concentrations in recreational users, but BE is higher in cocaine-related deaths. (2) Increased lung, liver and spleen weights are consistent with cocaine induced heart failure, but (3) Decreased BMI and increased heart weights in CTOX must be a consequence of long term cocaine use. Cardiac alterations may explain why equal blood cocaine concentrations may be lethal in some cases and innocuous in others, (4) Isolated measurements of postmortem cocaine and BE blood concentrations cannot be used to assess, or predict toxicity.

KEYWORDS: forensic science, forensic pathology, forensic toxicology, postmortem blood levels, cocaine, benzoylecgonine, toxicity, cause of death, cocaethylene, myocardial hypertrophy

According to government sources, more than 50,000 cocaine-related deaths have occurred in the United States during the last decade (1). Given such a large number of cases, it is somewhat surprising then that a relationship between postmortem cocaine blood levels and toxicity has yet to be established. Indeed, the subject remains a matter of considerable debate.

Earlier studies have either (a) included subjects who had used multiple drugs, (b) combined cases where death was a direct consequence of cocaine toxicity with other cases where cocaine was an incidental finding, (c) failed to account for sex differences, (d) generally ignored the problems of postmortem redistribution and postmortem degradation, and (e) rarely attempted to correlate toxicologic measurements with medical historical data and autopsy findings.

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Received 29 Jan. 1997; and in revised form 16 April 1997; accepted 9 May 1997.

In order to isolate some of the confounding variables, we studied autopsy and toxicology findings in a large group of men whose deaths were deemed to be the result of cocaine toxicity, and compared the results with findings in a control group of cocaine-using men where trauma, not cocaine, was the cause of death.

Materials and Methods

The records of the San Francisco Medical Examiner, from 1989 to 1995, were reviewed for cases where postmortem testing disclosed the occasional presence of alcohol, but no other illicit or prescription drug except cocaine and its metabolites, where cocaine (C) and benzoylecgonine (BE) were measured in both blood and urine, and where a complete autopsy was carried out. Cases where lidocaine had been given during attempted resuscitation ($n = 5$), were also included.

These cases were then divided into two groups: accidental deaths where death was ruled to be the direct result of cocaine toxicity (CTOX), and a control group of trauma-related deaths, both accidental and homicidal, where the presence of cocaine and its metabolites was deemed to be an incidental finding (TRAU). A total of 48 men and 6 women with cocaine-related deaths, meeting the above criteria, were identified. Because of their small numbers, the women were not included in the study. Sixty-five other cases were identified where cocaine was an incidental finding in trauma victims (TRAU). Fourteen of these were women, and they were also excluded, leaving 51 men dying of trauma, who incidentally were found to have been cocaine users. Table 1 shows the cause of death in the trauma cases. Table 2 presents the comparison of autopsy findings in CTOX and TRAU.

The collection site for blood samples was not noted in all the records, but general practice at the office of the San Francisco Medical Examiner includes the collection of blood from the right heart, and urine, for and EMIT screening. Gas chromatography with mass spectrometry is used to measure blood drug levels only after compounds are identified in the urine. Urine concentrations are also quantitated using GC/MS.

TABLE 1—*Causes of death in trauma control group (*n = *51).*

Causes	#	%
Fall from a height	1	1.6
Strangulation	1	1.6
Burns	2	3.9
Stabbing	3	5.8
Exanguinating hemorrhage (suicide)	3	5.8
Blunt head trauma	4	7.8
Gun shot wound	37	72.5

TABLE 2—*Comparison of autopsy findings in CTOX and TRAU.*

Physical Finding	CTOX	TRAU	*p*
Age	35.9 y	34.8 y	.549
Body Mass Index	24.6	30.6	.0001
Lung weight	1275 gm	1007 gm	.009
Liver	1896 gm	1628 gm	.008
Spleen	193 gm	146 gm	.001

During the period covered by this study, a benzoylecgonine concentration of 150 ng/mL was used as the standard cutoff for EMIT urine testing. GC/MS protocols were based on the original protocols of Griesemer, et al. (2). Cocaethyelene is not measured separately in our laboratory. But, since samples are derivatized with an acetified ethanolic solution, any cocaethylene present in a sample would be quantitated with benzoylecgonine. Limits of detection are 0.01 μgm/mL, operating in selective ion mode.

Blood and urine alcohol levels were measured using gas chromatography with flame ionization detection with a CARBOWAX 20M on 60/80 CARBOPAXK $^{1}/_{8}$ in. stainless steel column. Aqueous secondary alcohol standards are referenced to a NIST primary potassium dichromate standard.

The number of hours elapsed from time of death and time of specimen collection at autopsy was determined by reviewing records for each case. When possible, time of death was estimated from reports of death scene investigators. Time of autopsy was obtained from individual autopsy records. Cases with prolonged resuscitation attempts were excluded from consideration, as were cases where the time of death could not be estimated with any precision.

Statistical Analysis

P-values for two sample, two-sided t-tests between the two groups were calculated for each measured variable with alpha level = 0.05. Regression analysis was used to assess the relationship between cocaine and benzoylecgonine, and blood to urine ratios of cocaine and benzoylecgonine, in both the CTOX and TRAU groups.

Findings

The mean age in both groups of men was similar, 35.9 years in CTOX and 34.8 years in the TRAU group, $p = .549$. Alcohol was more frequently present, and at higher levels, in the controls than in the CTOX group ($p = .05$). Screening disclosed the presence of ethanol in only 7 of CTOX decedents (.03, .05, .06, .07, .110, .120, .180 gm/dL), but in nearly a third of the TRAU controls (14/51, mean level .072, SD = .010, SE = .005).

Findings were significantly different for each physical characteristic measured. The CTOX group had a lower Body Mass Index (24.6 vs 30.6, $p = <.0001$), and larger hearts (426 vs 369, $p = .009$) than in the TRAU control group. Lung, liver, and spleen weights were also greater in CTOX (1275 gm vs 1007 gm, $p = .009$, 1896 gm vs 1628 gm, $p = .008$, 193 gm vs 146 gm, $p = .001$) than in TRAU. Figure 1 is a scattergam illustrating the differences observed in Body Mass Index. Figure 2 illustrates the significant differences observed in heart weights.

Elapsed time intervals in the CTOX and the TRAU control group were similar. In 10 of the CTOX cases, and one of the TRAU control cases, times were either not recorded or were deemed unreliable. The mean time elapsed, from death until autopsy, in the CTOX group was 18.9 hours (SD = 8.14, SE = 1.27 hours). In the TRAU control group, the mean time was 15.7 hours (SD = 8.36, SE = 1.17 hours). The difference was not significant ($p = 0.0646$).

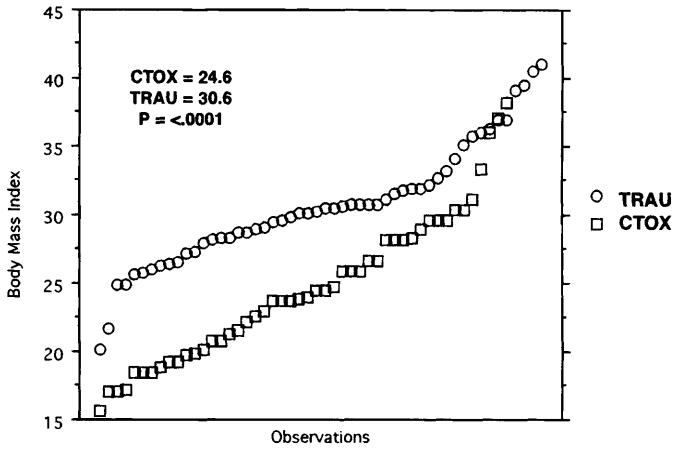

FIG. 1—*Scatter plots illustrating values measured in the two experimental groups for Body Mass Index [weight in kg/ht in meter]. CTOX and TRAU form two very distinct populations, with a value of 24.6 in CTOX and 30.6 in TRAU,* p = *.0001. Decreased BMI may reflect weight loss due to chronic drug use. CTOX are represented by squares, TRAU by circles.*

The mean blood cocaine concentrations in CTOX and TRAU were 1.12 mg/L ± 2.71 (SE = .39) and .487 mg/L ± .75 (SE = .10) respectively. These values were not significantly different ($p = .10$). However, mean BE concentrations were higher in CTOX than in the TRAU group (1.54 mg/L ± 1.68 (SE = .24) vs .946 mg/L ± .86 (SE = .12), $p = .026$). Urine concentrations of C and BE in the two groups were not significantly different (CTOX cocaine = 40.1 mg/L ± 83.7, (SE = 12.1), TRAU cocaine = 30.0 mg/L ± 83.3, (SE = 5.3), $p = .435$, and CTOX benzoylecgonine = and 58.2 mg/L ± 94.0 (SE = 13.6) vs 64.2 mg/L ± 65.0 (SE = 9.0), $p = .70$). Values are summarized in Table 3, and individual scatter plots for each category are shown in Figs 3, 4, 5, and 6.

Regression analysis disclosed that, within the CTOX group, linear relationships (at an alpha level of 0.05) existed between blood cocaine and benzoylecgonine concentrations (r = .462), urine co-

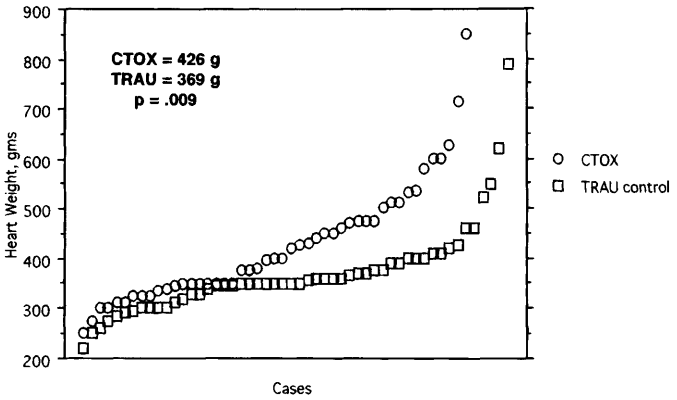

FIG. 2—*Scattergram illustrating the marked differences between CTOX and TRAU observed in heart weights. Squares represent controls, circles represent cocaine-related fatalities. Differences between the two groups were highly significant (*p = *.009), and it is clear that two different populations are represented.*

TABLE 3—*Comparison of toxicology findings in CTOX and TRAU (results in mg/L).*

Analyte	CTOX Mean	CTOX Range	TRAU Mean	TRAU Range	*p*
Blood Cocaine	1.12 ± 2.71	(.001–18.1)	.487 ± .75	(0–4.7)	.100
Urine Cocaine	40.1 ± 83.7	(0–468)	30.0 ± 83	(.07–157)	.435
Blood BE	1.54 ± 1.68	(0–7.7)	.946 ± .86	(0–4.09)	.018
Urine BE	58.2 ± 94.0	(0–517)	64.2 ± 65	(.24–228)	.700
Blood Coc/Urine Coc	0.242 ± .81	(0–5.6)	0.048 ± 0.9	(0–.643)	.100
Blood BE/Urine BE	0.151 ± .30	(.01–1.8)	0.044 ± .07	(0–.5)	.018

caine and benzoylecgonine concentrations (r = .533), blood benzoylecgonine and urine benzoylecgonine concentrations (0.480), and the blood to urine cocaine, and blood to urine benzoylecgonine concentrations (r = .890). Similar analysis of the TRAU control group showed higher correlation coefficients for the same pairs of variables (r = 0.653, 0.688, 0.625, respectively). However, the correlation coefficient for blood to urine cocaine and benzoylecgonine concentrations was lower (r = 0.301). This discrepancy persisted even after two extreme outliers in CTOX and TRAU were discarded and the regression curves recalculated, with r = 0.758 (r2 = 0.575) for CTOX and r = .71, (r2 = 0.50) for TRAU control.

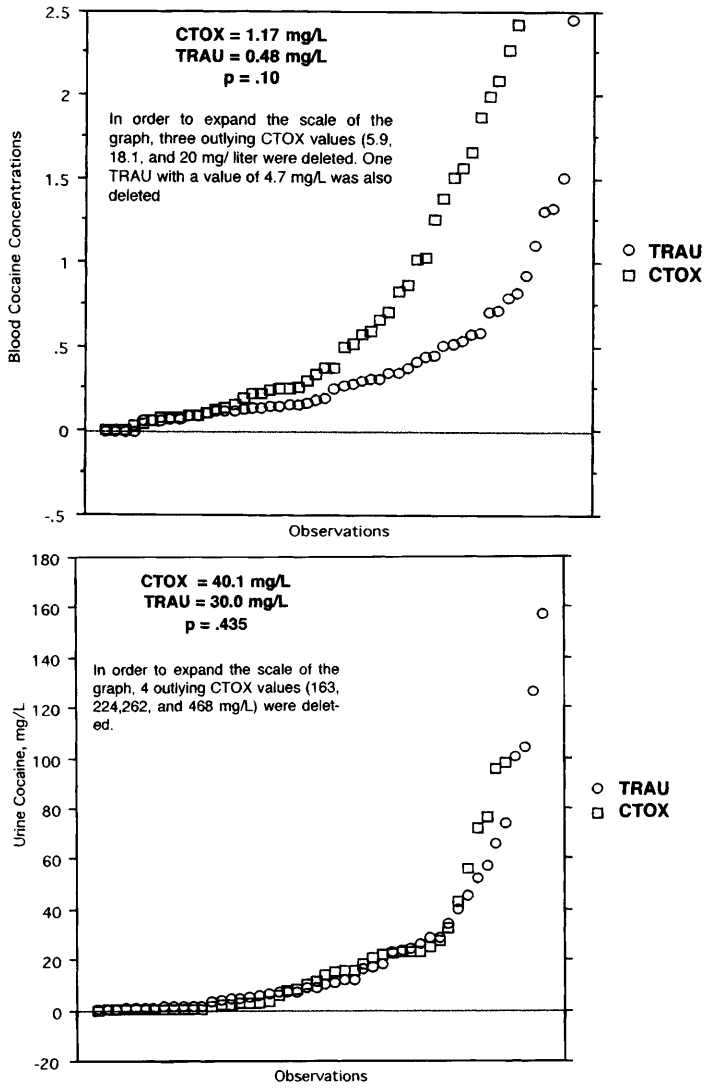

FIG. 3 and 4—*Scatter plots illustrating values measured in the two experimental groups for blood and urine cocaine. CTOX values are represented by boxes, the TRAU control group by circles. There was a trend to higher blood cocaine concentrations in CTOX, but differences were not significant for either blood or urine.*

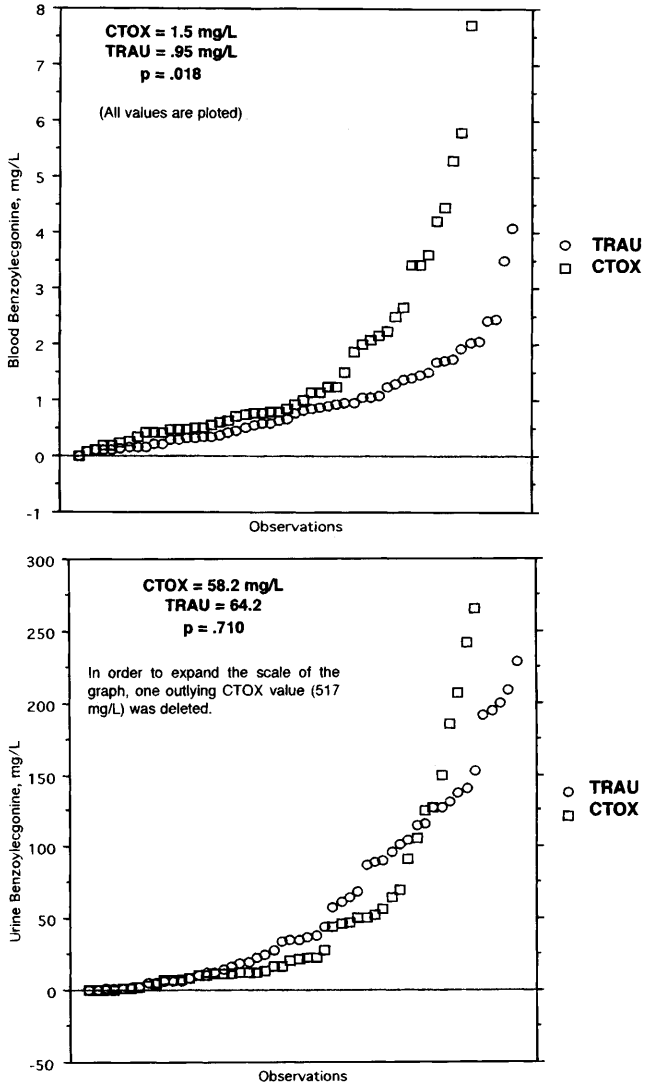

FIG. 5 and 6—*Scatter plots illustrating values measured in the two groups for blood and urine benzoylecgonine. CTOX values are represented by boxes, the TRAU control group by circles. Blood benzoylecgonine levels were significantly higher in the CTOX group, but urine concentrations were the same in both.*

Discussion

Physical differences between the two groups were striking. The only similarity was the age of the men; 35–36 years. The Body Mass Index of the CTOX group was much lower than in the controls (24.6 ± 5.4 vs 30.6 ± 4.4, $p = <.0001$), while heart, lungs, liver, and spleen weights were all much heavier. The increase over control weights was very significant ($p = .009, .009, .008, .001$, respectively). Differences in the toxicologic findings were less dramatic.

Blood cocaine concentrations in the cocaine-related deaths were not significantly different from concentrations observed in the control group. Cocaine concentrations in both groups were comparable to those reported in previously published autopsy studies (3–7). Substantial amounts of cocaine and benzoylecgonine were found in the urines of both groups but not in significantly different concentrations.

Blood BE concentrations were also comparable to those seen in earlier studies, but BE concentrations in the CTOX group were significantly higher than in the controls. The fact that the elapsed time from death to autopsy was essentially the same in both CTOX and TRAU adds further support to the notion that differences in blood BE concentrations between the two groups are real, and not artifact.

Explanations for the anatomic findings are readily apparent. Decreased BMI and increased heart weight are well recognized complications of chronic cocaine and stimulant abuse (8–13). Decreased BMI in the CTOX group reflects weight loss. Cocaine shares with other anorectic agents, such as amphetamine, phenylpropanolamine, and dexfenfluramine, the ability to alter the metabolism of serotonergic neurons involved with appetite control (8). Indeed, some of these agents are legitimately prescribed to promote weight loss.

Increased heart weight in the CTOX group is consistent with the results of previously reported clinical and autopsy studies (8–13). Cardiomegally in chronic cocaine abusers is thought to be a result of long term excessive catecholamine stimulation (11) with circulatory overload (14). However, the direct activation of immediate early genes has been demonstrated in the myocardium of cocaine treated animals (15), raising the possibility of some direct cocaine effect leading to myocyte enlargement.

The increase in heart size is highly significant. While the underlying mechanism in most cases of cocaine-associated sudden death appears to be cardiac arrhythmia (11), the results of the most recent animals studies suggest cocaine makes lethal episodes ventricular fibrillation less, rather than more, likely (17,18). The observation is hardly surprising since cocaine possesses all of the characteristics of a Class I antiarrhythmic agent (19). Left ventricular mass, on the other hand, is a known independent risk factor for sudden death, even in the absence of drug abuse (20–22). The relationship seems to be even stronger when cocaine is present (11).

The increased weight of the lungs, liver, and spleen in the CTOX group is almost surely the result of cocaine-induced heart failure with passive visceral congestion, a stereotyped finding in a variety of drug-related deaths (23–24). However, given the design of our study, structural alterations in the liver and spleen, secondary to long term cocaine abuse, cannot be ruled out. Other than passive congestion, abnormal liver pathology was not initially noted in these cases, however sections were not available for every case, and a reexamination of histologic alterations in the liver was not undertaken.

Explanations for the toxicologic findings are, for the most part, equally uncontroversial. Large amounts of unmetabolized cocaine were detected in urine samples from both groups, even though it has been suggested that only small amounts of unmetabolized cocaine appeared in the urine, and then not for very long (25,26). Most routinely employed screening immunoassays utilized antibodies against BE, and not cocaine, so that urine cocaine concentrations are hardly ever reported. It is now clear, however, that whenever large amounts of BE appear in the urine, cocaine in substantial quantities will also be found. Ramcharitar et al. reported that 83% of postmortem specimens containing more than 2 mg/L of benzoylecgonine also contained cocaine (7). Urine cocaine and BE concentrations reported here are consistent with Ramcharitar's observations.

A substantial overlap between "recreational" and toxic cocaine blood concentrations is also a well recognized phenomenon, usually attributed to the development of tolerance (27), although just what that process involves has never been clarified (28). Clearly, some of this "overlap" may be more apparent than real. Cocaine and benzoylecgonine concentrations measured at autopsy are obviously a function of dose, the time elapsed from the last dose until the time of death, and the time elapsed from time of death until specimen collection. But there are other confounding factors as well.

Previous autopsy studies have comingled cocaine users with poly drug abusers and/or body packers (29). Others have admixed results in men and women (3,4), even though is now clear that men and women metabolize cocaine differently (30). The inclusion of both sexes in the analysis is just as likely to confound the final result as including individuals who are taking two different drugs. Similar confusion results from the comingled values measured in trauma victims incidentally found to have used cocaine, with other values measured in patients dying from cocaine-related toxicity (3,31).

But even when the obvious confounding variables are taken into account, as they were here, the range of values observed is still very wide, suggesting that other factors must be involved. Cocaethylene production may be one factor (32,33). Mounting clinical evidence suggests that cocaethylene formation may lead to increased toxicity when cocaine and ethanol are ingested simultaneously (34), although this connection has not been firmly established. However, even if the presence of cocaethylene does enhance toxicity, in the current study, more of the TRAU control group had alcohol detected than the CTOX group, so the confounding effect of cocaethylene formation, would appear to be minimal.

Another factor might be cocaine storage in deep body compartments. Hospitalized abstinent cocaine abusers, under strict observation, continue to excrete measurable quantities of cocaine for weeks after their last dose (35,36). Similar considerations apply to benzoylecgonine, although the situation is not nearly so well studied. The results of animal experiments suggest that there are limits to the amount of cocaine and benzoylecgonine that can be stored in tissues. Benzoylecgonine concentrations measured in rats treated continuously with cocaine for one month, exhibit step wise increases, suggesting that receptors and tissue storage depots become saturated (37). In this study, blood benzoylecgonine concentrations were significantly higher in CTOX than in TRAU, and the correlation coefficient for blood/urine ratios were also greater than for controls.

A plausible explanation for these findings is that decedents in the TRAU group still had room to store cocaine in their bodies, but that CTOX patients did not. In other words, data from the CTOX group might best be described by a one compartment model. When TRAU patients ingested cocaine, much would have gone into peripheral compartments and the blood/urine BE ratio would not remain linear. Pharmacokinetics in the TRAU control group would best be described by a multi-compartment model. The major difficulty with this explanation is that ecgonine methyl ester (EME) concentrations were not measured in our study. Without actually measuring this other metabolite, there is no way to know whether or not a similar proportion of cocaine is converted to BE in both groups.

In living patients there is, at least, a fairly good correlation be-

tween cocaine blood concentrations and some physiologic responses, such as pulse and blood pressure (38), providing that tolerance has not occurred. After death, the situation becomes much more complicated. Tolerance cannot be assessed, and postmortem redistribution and metabolism may result in blood concentrations higher, or lower, than they were in life. Even if redistribution and postmortem metabolism were not a reality, there still is no way to determine how accurately a single blood level measurement reflects the equilibrium between central and peripheral compartments.

Pathologists and toxicologists asked to determine the role of cocaine in cases of accidental deaths face a formidable task. More often than not, they have no idea how much drug was ingested, or when it was taken in relation to the time of death. Thus, even though our study shows that blood BE concentrations are higher in cocaine-related deaths than in cases where cocaine is an incidental finding, cocaine blood concentrations in the two groups are indistinguishable, and benzoylecgonine values overlap substantially. Postmortem cocaine and BE blood concentrations, in isolation, are not sufficient to determine the cause of death, especially given mounting evidence that postmortem cocaine and metabolite concentrations bear no predictable relationship to perimortem concentrations (39). In order to make a rational determination, autopsy findings, along with the reports of scene investigators, must also be considered. Even then, an accurate determination may not always be possible.

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