Criteria for the Interpretation of Cocaine Levels in Human Biological Samples and Their Relation to the Cause of Death

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Abstract: The determination that cocaine is directly responsible for the immediate cause of death should be considered only when there is a reasonably complete understanding of the circumstances or facts surrounding the death. Another, more obvious and immediate cause of death must be absent, or, at least cocaine must be shown to be a significant contributing factor in the chain of medical findings that lead directly to the immediate cause of death. Not all death investigation requires the sequential steps described in this paper, but these steps must be considered early on in the investigation whenever there is scene, investigational, medical or a historical basis to believe that cocaine is directly related to the cause of death. A relatively high profile death when cocaine is known to be involved, or a death involving unusual behavior on the part of the deceased with police involvement are examples where these considerations may well apply. Information needs to be obtained as soon as possible to have the highest chance of successfully documenting the toxicologic basis for the diagnosis. These facts would include, but would not necessarily be limited to, a scene investigation (whenever possible), a careful review of the investigative reports from all involved agencies, the initial core temperature of the body as well as that of the environment at the time of the collapse or death, the past medical history of the individual, and the results of a complete forensic autopsy and toxicologic studies. Knowledge of and an understanding of the current relevant forensic literature on this subject should be available to the reviewer prior to any interpretation of the significance of cocaine upon a specific death.

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Cocaine is the alkaloid extract from the leaves of the coca plant, *Erythroxylon coca.* Although the plant will grow almost anywhere in the world, today, South America is the only current large producer of the drug. At the turn of the last century, cocaine was a major cash crop in Java, Taiwan, Okinawa, India, Ceylon, and even Nigeria, but worldwide production, prior to World War II, never exceeded 10 tons. Current levels of South American production are now thought to be approaching 500 tons per year.[1] The harvesting of the leaves and the drug extraction process are very labor-intensive involving principally hand labor. These facts, along with the interdiction policies of countries like the United States, keep the clandestine production limited to remote areas. According to published data, about a third of all adult males arrested in the United States during 1998 were positive for cocaine, more than 77,000 cocaine-related emergency room visits occurred during the first half of 1999, and nearly 5000 cocaine-related deaths were reported to the DAWN survey in all of 1998.[2] The 1998 National Household Survey on Drug Abuse presents that cocaine had been reportedly used by 3.8 million Americans. With so many Americans using cocaine, the drug is frequently detected at autopsy, and its contribution to morbidity and to the cause of death is an increasingly common forensic issue. Perhaps it is because so many deaths have occurred and the effects of the drug have been such an issue that a better understanding of the neurophysiology of cocaine toxicity has begun to emerge. Today, the neurochemistry of cocaine toxicity in human brain has been characterized,[3,4] and the effect of cocaine-mediated catecholamine induced excess upon the heart is now better appreciated.[5] But, as the accompanying cases illustrate, none of these factors

can be considered in isolation without a review of the other elements of the case.

Deciding that the death is drug related is done after reviewing all available information gathered from the scene, autopsy, laboratory and the medical history. Cocaine is considered directly related to, or the underlying cause of death, when one or more of the following is true:[1] The circumstances surrounding the death can be associated with a high dose acute cocaine exposure, and an obvious supervening disease process which produced anatomic or histologic changes that would likely lead to death is absent. These deaths represent an acute drug poisoning. Since the drug directly leads to death, these findings are considered to result in an accidental or, in an unusual circumstance, homicidal manner.[2] The immediate cause of death is obvious, but cocaine is considered to be the underlying cause of the death. Trauma may be the immediate cause of death, for example, with cocaine being the reason for the person being subjected to that trauma (eg, an agitated delirium person running in front of a car). These deaths are typically listed as accidental or homicidal in manner, depending upon all the circumstances associated with the investigation. They do not usually meet the requirements to be designated as suicidal.[3] Chronic cocaine use leads to recurrent catechol induced tissue changes that result in a pathologic process leading to death. In accordance with World Health Organization recommendations and the guidelines for death certification recommended by the Centers for Disease Control, these findings result in the death being listed as a natural manner because of the chronic nature of the drug exposure.

Toxicologic studies, which may include the analysis of neurotransmitters in the frozen midbrain, chemical analysis of tissue, hair or other ante and postmortem biologic samples, often reveal findings that differentiate between acute or chronic cocaine use. The levels of the drug and its principal metabolites may or may not be related to direct poisoning, but because of the effects on the cellular and neurotransmitter mechanism of the midbrain, the drug can directly cause death through a pathway other than that of acute drug poisoning or toxicity. Because of the process of postmortem drug redistribution and the fact that the toxic effect of the drug is on the neurotransmitter process, actual blood or urine levels do not necessarily prove or disprove the presence of a direct drug effect.

Cocaine is known to be atherogenic. Histologic studies of the heart often reveal acute and chronic myofibril necrosis or fibrosis as well as small vessel wall thickening. These are histologic changes commonly associated with cocaine-induced disease. Myofibril necrosis is microscopic and may involve only part of an individual fiber (ie, cross-band necrosis). The anatomic or histologic changes of chronic use (eg, coronary artery stenosis, focal myocardial scarring, etc.) are usually considered to result in a natural death. Chronic cocaine abuse, when known, could be listed as a contributory cause but would not be listed as directly related to the death.

SCENE INVESTIGATION

Ideally, the investigation into the death starts at the scene. Is the deceased still there or has he/she been transported to the hospital? If the deceased is at the scene, the investigator looks for and notes the presence or absence of sweating, the original position of the deceased at the time of death, the type and nature of the clothing, the presence of any restraints, and the skin and body core temperature. The nature and the anatomic location of the restraint are noted. What has been changed or removed from the body? What were the behavior, appearance and speech pattern of the individual? Were there any signs of or information about bizarre behavior, struggle with family, neighbors or the police at the time of death, since restrictive or another form of asphyxia needs to be considered. The use of pepper spray, stun guns, Taser, or any blunt force is noted as well, since these items can require additional studies during the investigation or autopsy. Information is obtained from eyewitnesses, paramedics, police or others who interacted with the deceased. If the family is known, then they often are a source of information about the past medical history and the location of medical records. The type of drug apparatus is usually reflective of the type of drug used, and the scene needs to be reviewed for the presence of pipes, syringes or drug containers.

If the deceased was resuscitated and transported from the scene, determining the circumstances surrounding the physical collapse is done by careful investigation. Statements of witnesses (audio or video taped if possible) are gathered. If photographs or videotaping took place during the incident, including film from security cameras, that material is reviewed.

If airway obstruction, restrictive asphyxia and trauma are issues, then understanding the circumstances from the scene prior to the autopsy is often beneficial. This is particularly true since the condition of the body will change with resuscitation or movement to a medical facility and the passage of time. If a struggle occurred, what was the sequence of the events? If the person was restrained, what position was he/she in, and what were the conditions and the duration of the restraint? If he/she was struggling, what was his/her behavior (rational and angry or agitated and delusional)? Was she/he having difficulty breathing with air hunger or stridor? Was sweating inappropriate for the prevailing weather conditions? Was there no sweating or rapid breathing even during a struggle? Was a chokehold used during the arrest, or were the police not involved? Did family or others physically restrain the patient?

An episode of agitated delirium is most often seen at the end of one or more days of drug use. Blood levels for cocaine may be low or even not detectable at that time. The

effects on the brain's neurotransmitters lead to a loss of thermoregulatory control and alter the thought process. If the patient isn't breathing rapidly, sweating and tired after a struggle with the police while at the same time the officers are all showing those changes, then there is a high likelihood of an impending collapse. There is some data to support that an agitated delirium event is not reversible.

Body temperature has a high correlation to a disordered central nervous system regulatory process, leading to the loss of thermal regulation and hyperthermia. This finding is strongly supportive of a cocaine-induced agitated delirium, but in itself is not a *sine qua non* for the diagnosis. In order for this supportive physical finding to be documented, a body core temperature must be taken as close to the time of death as possible. Noncore temperatures, such as skin strips, ear canal infrared measurements and skin palpation are not reliable and may be misleading. Other causes of hyperthermia must be eliminated. The paramedic form often includes only the check-off for warm skin. You may need to find the paramedics to learn if the skin was hot and dry, not just warm and dry.

Knowing what drugs or chemicals were used during resuscitation allows the investigator to differentiate medically caused changes from nonmedically caused changes. Although very rare, in an emergency setting, cocaine is sometimes used as a medical aid during intubation. Knowing the drug history for prescription and/or over-the-counter medications is also helpful.

Cocaine is now often found in the alkaline form as "crack cocaine" and is smoked. Clues at the scene include the characteristic pipes used to smoke the drug and the presence of numerous matches or multiple cigarette lighters with a relatively small number of consumed cigarettes. The pipes usually consist of a glass tube or pipe of various materials that has a plug of copper mesh within the tube or at the base of the pipe bowl. Crack cocaine appears as small fragments of firm compressed powder of irregular shape. The individual "rocks" are usually about ¼ to 3/8 inch in width. They are irregular in size and color, usually off white to buff and with variable shades in their color. The name for the drug comes from the characteristic popping or crack-like sound that is produced when the drug is heated during smoking. Smoking usually causes pyrolysis rather than sublimation of the chemical.

Features often seen on the chronic crack smoker are focal burns of multiple ages on the mucosa of the lips, the tip of the tongue, and the opposing skin of the fingers. The involved fingers are usually the palmar aspects of the thumb and the index finger. These heat injuries are produced from holding the hot glass pipe or getting too close to an open flame while repeatedly heating the pipe with a cigarette lighter. Rarely, the same process causes burnt hairs within the nose or singed eyelashes. The pipe is often charged with tobacco to help maintain the heat of pyrolysis, so that empty cigarette paper wrappers are left in the ashtray. In some cases, alcohol, heroin or other drugs are consumed at the same time, but most often, cocaine is used as the sole drug.

THE FORENSIC AUTOPSY

The external examination documents all positive and negative physical findings. Frequent cocaine users occasionally develop a callus upon the palmar surface of their thumbs from "flicking" the cigarette lighter frequently to keep the "rock" hot. A thin ring of white or light brown powder can sometimes be seen at the external nares when the drug is snorted. This material can be collected with a little methanol or chloroform onto a swab. Since "snorting" the water-soluble salt is now relatively uncommon, nasal septum perforations are rare. Specific attention is paid to the parts of the body often associated with needle injection sites. The area of the neck deserves close attention, since an allegation of asphyxia can be an issue in these cases.

The collection of specimens should be done as soon as reasonably possible following the death. Antemortem or resuscitation specimens are often most helpful if the patient is placed upon a respirator or resuscitated for any length of time. Blood should be collected by needle and syringe from peripheral vessels. Direct aspiration with a needle inserted into the confluence of the vessels at the root of the neck or the femoral vessels is an easy technique that allows for the rapid collection of peripheral blood specimens. This can be performed by percutaneous aspiration immediately following the death if there is going to be a delay in the performance of the autopsy examination. When collected during the autopsy, the extremity vessel is tied or clamped off and the sample aspirated distally to the clamp to collect peripheral blood only. Generally, central or heart blood is avoided for forensic toxicology specimens unless that specimen is specifically needed or there is no other option. Postmortem redistribution and diffusion from the lungs or gastrointestinal regions make this a less than desirable specimen. As a general statement, central vessel blood is not relied upon alone for detection, quantitation and the interpretation of any drug level. If possible, at least 2 separate samples are collected. The collected blood samples are stored mixed with sodium fluoride at a final concentration of between 5 and 10 mg/mL and stored for analysis. The samples can be stored refrigerated, but samples are most stable acidified and frozen.

It is critically important that adequate samples be collected for toxicologic analysis whenever you have reason to suspect the potential of a drug related death. The samples can be collected and, if it turns out that drugs are not an issue, the samples can just be stored for eventual destruction. However, it is almost impossible to go back after the passage of time or the completion of the autopsy, and collect most of the necessary samples. For example, the brain needs to be collected as soon as possible after death. Ideally, this should be

within 6 hours, but no longer than twelve hours following the death. Bile, urine, spinal and vitreous fluids are all often destroyed during the examination. Gross contamination with stomach or bowel content is a real issue. Therefore, it is critically important to sequentially collect the specimens, protect them from contamination or damage and to store them properly whether you actually analyze them or not. In this manner, you protect the evidence for your analysis or that of another investigator.

Samples of plucked head hair (from at least 2 areas of the head with apical roots attached) and fingernails can be collected at this time. These can be stored frozen or at room temperature. Spinal fluid is collected by cisternal puncture prior to the autopsy. Vitreous can be collected after the eyes are physically examined. Re-examination following the aspiration of the vitreous fluid allows for a more detailed examination of the sulcus in many cases. Microscopic or histochemical studies of skin injuries may be necessary, in some cases, to form a basis for a statement of the time of the injuries relative to the time of death.

Unless trauma or vascular rupture is found, cocaine related autopsies are usually negative during the gross dissection for a finding of a significant pathologic process explaining the death. As with other negative autopsies, gathering adequate samples for microscopic and toxicologic examination is important. Usually, bile and urine are collected by aspiration before the organ samples are collected, helping to reduce the potential for contamination of these specimens. The bowel lumen is examined in its entirety to evaluate the possibility of ingested drug. Crack cocaine will dissolve in gastric material if left long enough but the water-soluble hydrochloride dissolves rapidly. One clue can be portions of wrapping material found within the bowel lumen. In this case, gastric or bowel contents are collected as a specimen. Individuals on the street often carry the "rock cocaine" in their mouths so that they can swallow the drug rather than be arrested by the police for possession of a controlled substance, so routine collection of gastric contents, regardless of their appearance, is a recommended procedure.

The entire heart is saved so that the conduction system can be examined along with portions of the myocardium and the valves. Other causes of sudden death, such as a hypoplastic aorta (diameter less than 2 cm in an adult) or valve leaflet rupture, can be evaluated at this time.

The lungs often have a characteristic heavy alveolar carbon deposit suggestive of an acute particle inhalation. This looks grossly like a terminal aspiration of blood, but the multifocal deposits are black. The change represents the inhalation of large amounts of carbon particles along with the drug. Smokers often inhale as hard and deeply as they can to get a large dose of the drug, also inhaling the carbon particles from the pipe and its contents.

The brain, if it is going to be collected, is processed as described below. Rapid freezing is important. Only half of the brain need be submitted for the neurotransmitter marker analysis and then only if the rest of the examination supports the need for that test. A posterior cranial and neck approach often allows for a complete examination of the brain as well as the posterior neck, upper spinal cord and the vertebral arteries.

The neck is examined last to avoid any potential artifact in the form of hemorrhage into the muscle or soft tissue. A careful layer-by-layer dissection is necessary to find any minor hemorrhage or trauma. Examination includes the muscles of the lateral neck and the prevertebral fascia. The structures of the larynx require careful and full dissection, including the tongue and posterior pharynx.

Forensic samples for drug analysis

A. Hair for evidence of chronic abuse

Although agitated delirium appears to be associated only with the chronic use of cocaine, hair analysis can be used to resolve the question of whether death was related to a first episode of drug use or regular drug use. Hair analysis can demonstrate multiple deposits of the drug along the length of the hair shaft, thereby supporting chronic use. Samples are pulled from more than one area of the scalp and stored at room temperature. Currently, about 50 to 100 mg of hair is generally required for analysis, but the specific requirements of the selected reference laboratory may vary. More laboratories are becoming qualified in hair drug testing with most methods requiring gas or liquid chromatography coupled with mass spectroscopy. An immunochemical method is in development but is not in general use. Interpretation is qualitative, more related to evidence of exposure rather than quantitation. Even when drug use is not initially suspected as a cause of death, many feel it advisable to collect hair and retain the samples in the event that that question should arise.

B. Admission samples of blood and urine-stability of cocaine

Every effort should be made to obtain the earliest antemortem samples, especially those collected by the paramedics. Cocaine measurements in post mortem specimens do not necessarily reflect values that existed at the time of death. This is especially so if resuscitation is lengthy. Postmortem redistribution occurs, as does the continuing conversion of cocaine into its metabolites. But specimens collected during resuscitation and preserved with sodium fluoride may provide a much more accurate picture of the situation in the immediate antemortem period.

C. Brain

The brain is removed and sectioned into coronal slices. Each reference laboratory has its own sectioning preferences. Some may prefer whole parasagittal sections, which they will

selectively sample for analysis. Another laboratory may prefer that you select a specific site for analysis. In either case, regions-of-interest are sampled from the brain slices for neurochemical analysis as described below. Factors, which can confound interpretation of the receptor site analysis, include agonal state, drug history, post mortem interval, and handling of the post mortem tissue. For neurochemical analyses, autolysis times must be less than 24 hours and, ideally, less than 12 hours from the time of death. Ensuring that the substantia nigra and the anterior sectors of the striatum are sampled for these studies requires special care. These regions contain cell bodies and terminals of the mesolimbic dopaminergic system. The substantia nigra is taken at a level through the posterior commissure, medial and lateral geniculate bodies, and the red nucleus. The striatum is sampled at an anterior level, which includes the nucleus accumbens.[5,6]

Benzoylecgonine found in the brain was formed in the brain, since this compound does not effectively cross the blood-brain barrier. This information is helpful in interpreting the findings as to an acute or chronic exposure. Because of the blood-brain barrier and specific binding sites, brain tissue sampling can reveal information on the acute or chronic use of the drug, and potentially the effect upon the neurotransmitter sites that could lead to an interpretation of the behavior and death. High brain concentrations of cocaine but low or absent metabolite levels indicates a recent exposure, while the presence of benzoylecgonine but no parent compound establishes the passage of time or suggests chronicity of use. In some European offices, brain stem morphine concentrations are preferred to blood concentration measurements because they are thought to more accurately reflect the situation at the time of death (metabolism stops when blood flow ceases). This same argument may be true for cocaine.

In cases of suspected agitated delirium, where neuroreceptor and neurotransporter receptor measurements are desired, one cerebral hemisphere is coronally sectioned into one-centimeter thick slices. The brain slices are rinsed with physiologic saline, placed on a plastic sheet, flash frozen with liquid nitrogen or on dry ice. The samples can be stored in a −70°C freezer until the decision is made to send the samples for neurochemical analysis. Shipping is made on dry ice.

D. Peripheral blood and importance of preservative

Because of native esterases present in blood and serum, cocaine continues to be converted to benzoylecgonine even after death. A preservative, such as sodium fluoride at levels of 5 to 10 mg/mL, effectively inhibits this conversion process, but it will not prevent the pH-dependent (alkaline) hydrolysis that occurs over time. Blood samples preserved with NaF are stable for one week in the refrigerator and at least 3 months in a freezer. Frozen samples of brain are typically stable for at least 6 months or longer. Inferior vena cava or heart blood is used for toxicologic testing only when no other blood sample is reasonably available. All basic drugs redistribute from the lungs, through the thin walled pulmonary veins, into the left ventricle, falsely elevating drug concentrations. Blood from the right ventricle appears to be the more reliable option if blood must be collected from the heart.

E. Urine

This sample lends itself to an easier extraction or analytical path than do many other biologic samples, allowing the toxicologist to screen for a variety of metabolites and other chemicals. Cocaine is eliminated in urine for many hours or even days following a single exposure. It can be present for a week or more in chronic users. It is not possible to specifically determine the degree of intoxication or the significance of a specific drug level from quantitation of urinary cocaine concentration or the concentration of any of its metabolites. It is also difficult to determine acute or chronic use from a single urine analysis, since the ratio of parent to metabolite is altered by repeated drug exposures. However, a large amount of cocaine with a relatively small amount of metabolite is suggestive of a recent exposure, while the reverse is supportive of chronic use followed by a period of abstinence. Although the bioconversion of cocaine to the metabolite in urine is absent or slow, a preservative helps retard that process. Hydrolysis is minimized by acidification of the specimen. So far, there are no reports of a microbe that metabolizes cocaine as a food source.

F. Bile

Bile can be useful in some cases where decomposition has occurred or there has been a long delay from the initial incident to autopsy, as in a case where the individual has sustained hypoxic brain damage and has been maintained on a ventilator for many days. In these cases, hair testing may provide a better alternative.

G. Spinal fluid

Spinal fluid is somewhat protected, and the detection of cocaine can be helpful when acute blood loss leads to significant blood transfusions or fluid replacement, the passage of time during resuscitation is brief, or to help confirm the validity of blood levels. This specimen also allows an evaluation of the ratio of cocaine to benzoylecgonine. The latter does not cross the blood brain barrier to any extent, and therefore was formed in the brain from cocaine. The value of analysis of other metabolites is not yet fully established.

H. Vitreous

There are few studies on the rate of distribution of cocaine into vitreous. The principle value of this sample is detection when other samples are not available, are poten-

tially contaminated, or altered by medical treatment. Interpretation is limited to the presence of the drug.

I. Drug residue

Samples collected from potential drug delivery sites, including nasal, oral, vaginal and rectal areas, can support an acute toxicity diagnosis. Wrapped or unwrapped cocaine, as the salt or the base, may be found in the bowel lumen. Cocaine is most typically seen as a powder when it is the hydrochloride salt, or as a granule or small chunk of material when it is present as the base. Liquid forms and solutions are now uncommon. Samples of the drug can be recovered for analysis from the delivery device, such as a pipe, a "tooter," or a syringe. Chemical analysis of a solvent washout of these devices or from a container will detect the drug but not necessarily prove that it was used.

There are regional differences in both the form and the use of the drug. Cocaine salt is usually sold in small plastic "zip-lock" bags or paper bindles, while the base is often wrapped in plastic, household-style kitchen material or within small rubber balloons. Cocaine, as a salt, is water-soluble and is snorted or injected. Cocaine base is much more fat soluble, and when smoked gets to the brain in seconds. Even though the principal material is gone, a chemical extract, swab or scraping can be analyzed to identify the presence of the drug. This information may not prove the form of the drug that was used, but once the drug in the body, the effects caused by either form are similar.

Preservative

Studies demonstrate that cocaine continues to break down into benzoylecgonine in whole blood, and at a slightly slower rate in plasma or serum. This change is particularly true for samples stored at room temperatures. Sodium fluoride, at the final dilution level of 5 to 10 mg/mL, restricts the conversion rate and slows the process significantly.

Other preservatives, such as mercury compounds and mercury salts exist but are very seldom used in modern forensic medicine. Mercury salts are toxic and require very special handling of the specimens so their use is impractical or illegal. The waste material has to be destroyed in an approved waste site. Other enzyme poisons are particularly toxic or require special handling, also making them impractical.

Physical preservatives

1. Refrigeration at 4 to 5°C will slow but not stop the enzymatic conversion. Freezer temperatures, especially lower than –20°C, are necessary to arrest the conversion process. Refrigeration of sodium fluoride treated specimens further slows the degradation process.

2. The low temperature provided by liquid nitrogen or dry ice effectively stops the chemical breakdown and is used to prepare samples for transport for neurochemical site analysis.

CASE HISTORIES

The following case histories illustrate the application of some of the principles described above as applied to actual cases.

1. A 19-year-old basketball player, 6 feet 3 inches tall, 250 pounds, collapsed during a tournament and could not be resuscitated in spite of immediate paramedic support. There was no known or reported history of drug use, and no significant medical history. Routine toxicologic testing was negative. Viral cultures and antibodies were negative. Positive findings were confined to the heart, which weighed 475 g. Concentric left ventricular hypertrophy was evident. The epicardial vessels were without disease, though there was a prominent aortic fat streak. There was no valvular disease and, even though the septum was somewhat thickened, there was no evidence of myofibril disarray. Microscopic examination disclosed perivascular fibrosis, thickening of the media in the small resistance vessels, and focal interstitial fibrosis with multifocal myonecrosis (contraction bands). No pheochromocytoma had been seen at autopsy. Toxicologic studies of blood, urine and liver were negative for drugs of abuse and common pharmaceutical compounds. The manner of death was initially ruled to be natural, a consequence of catecholamine toxicity, etiology undetermined. Six months afterward, a friend volunteered to the press that the individual had been a regular cocaine user. Hair samples, obtained at autopsy and kept in storage, were analyzed and found to contain cocaine along their length. The death certificate was amended to a natural death as a consequence of chronic cocaine toxicity.

2. A 35-year-old woman, 5 feet 6 inches tall, 100 pounds, was found dead in the street shortly after leaving a suspected crack house. She had a history of several arrests for prostitution, but her medical history was otherwise unknown. She was found lying on her face and had a small amount of congealed blood about the nose and mouth. The injuries to the mouth and face were consistent with a fall to a flat surface. At autopsy, the heart was enlarged and weighed 375 g. There was 90% obstruction of the left anterior descending coronary artery with a fresh thrombus overlying a ruptured plaque. No infarct was visible, but there was an intense population of myocardial contraction band necrosis, even in the territory served by the circumflex artery. Some areas of very focal fibrosis were seen in the left ventricular free wall. Blood cocaine was 1.2 μg/mL with a blood benzoylecgonine level of 5.8 μg/mL. Brain cocaine concentration was 6 μg/gm; brain benzoylecgonine was 1.25 μg/gm. The manner of death was deemed to be accidental, a result of coronary artery disease, which was a consequence of acute and chronic cocaine abuse. The very high brain cocaine

concentration and the low level of metabolite are consistent with use of the drug shortly prior to death and may well have been responsible for an episode of coronary artery spasm leading to plaque rupture.

3. A 27-year-old man, 165 pounds, who had no significant contributing medical history, was witnessed to collapse and have a generalized tonic-clonic seizure. According to the witnesses, he had been dancing just prior to his collapse. He was not known to have used drugs and had consumed only 2 beers. There was no trauma. His only known complaint was of recurrent headaches. He took no medications and had not seen a physician for more than 5 years. That visit was for a routine physical examination to serve as a counselor for a scout camp. At autopsy, his heart was of normal appearance and weighed 302 g. There was only minor arteriosclerosis of the coronary vessels and mild atheromatous streaking of the ascending aorta. The blood alcohol level was 0.02 g/dL, but the cocaine level was 0.25 μg/mL and the blood benzoylecgonine level was 0.17 μg/mL. Cocaethylene was not detected. There was acute hemorrhage within the brain, shown to be associated with a malignant glioblastoma. The cause of death was reported as acute cerebral hemorrhage, due to malignant glioblastoma multiforme. The manner was reported as natural. Although cocaine may have contributed to an increased systemic blood pressure, the nature of the tumor and the physical activity were judged to be the more significant factors in his death. Cocaine was listed as another significant finding contributory to the cause of death.

4. A 24-year-old man, 5 feet 10 inches tall, 265-pounds, with a history of multiple hospitalizations for cocaine and alcohol abuse, was caught while attempting to shoplift a laptop computer. When a security guard attempted to apply handcuffs, the suspect literally threw the guard through a plate glass window and then ran into the store parking lot where he wandered about aimlessly. The suspect was eventually restrained by 6 security guards and bystanders, with one or more holding on to each extremity and another holding on to the patient's head. All the while, the suspect, according to other bystanders, was "screaming in tongues" and sweating profusely, even though it was snowing outside the store and the air temperature was near zero. When the police arrived, they placed restraints upon his legs as well, sat the man up in the back of the police cruiser and took him to jail. The man continued to ramble incoherently on the way to jail, but became suddenly quiet while in the booking area, collapsed, and could not be resuscitated. At autopsy, performed 2 hours after death, the body core temperature was 104°F. There was no physical evidence of neck compression or trauma, and while there were acute bruises about both hands, wrists and feet, no bruising was apparent on the back, even after extensive dissection. The brain was removed, examined grossly, and the left hemisphere was cut into 1 cm coronal slices, placed on a steel baking sheet, frozen on dry ice, and shipped to a neurochemistry reference laboratory. The other hemisphere was fixed for later microscopic examination and was subsequently reported as unremarkable. The lungs were wet with a total weight of 2200 g. The heart weighed 610 g with was no gross evidence of an infarction. There were 50% occlusions of both the left anterior descending and the left circumflex coronary arteries, moderate medial hypertrophy of the small coronary vessels, and moderate focal interstitial fibrosis. Femoral blood was found to contain 0.45 μg/mL of cocaine and 2.4 μg/mL of benzoylecgonine. Brain cocaine was 2.0 mg/kg, while benzoylecgonine was 13 mg/kg. Receptor measurements failed to show the expected increase in dopamine transporter sites typically seen in nonpsychotic cocaine users, and there were decreased numbers of D2 dopamine receptors in the portion of the hypothalamus responsible for temperature control. Kappa receptors were increased in the amygdala. Although the death was described in the press as a case of "positional asphyxia," the manner of death was deemed to be accidental, with the cause of death listed as agitated delirium due to acute and chronic cocaine abuse.

5. A 45-year-old man, 6 feet tall, 200 pounds, an insurance executive with a history of hypertension, hyperlipidema and cigarette smoking, was witnessed to clutch his chest, and then collapse while playing tennis. He could not be resuscitated in spite of immediate CPR. An autopsy revealed 80% occlusion of the left anterior descending coronary artery, with 50% occlusion of the circumflex and right coronary arteries at their origin. In addition, there was a high-grade obstruction of the right renal artery. The heart weight was 425 g (predicted 336 g). The lungs were relatively dry (total weight 875 g). Microscopic examination of the heart showed no fibrosis, but there was evidence of myocyte hypertrophy and intense contraction band necrosis throughout the heart. Blood cocaine was 1.2 μg/mL and benzoylecgonine was 0.3 μg/mL in sodium fluoride preserved femoral artery blood. Brain cocaine was 3.2 mg/kg and brain benzoylecgonine was 0.5 mg/kg. Even though the individual died as a result of an acute myocardial infarction, the manner of death was ruled to be an accident resulting from presumed cocaine induced coronary artery spasm in an individual with pre-existing coronary artery disease. In the absence of other anatomic changes or history of cocaine use, and given the history of hypertension and hyperlipidemia, it can be presumed that the individual was at most an occasional drug user, and that the coronary artery disease was unrelated to drug use.

DISCUSSION

COCAINE METABOLISM

The half-life of cocaine in blood is considered to be about one-half to one and one-half hours.[7,8] The half-life of cocaine for chronic users may be significantly longer than

this, potentially approaching 4 hours. The half-life of benzoylecgonine does not appear to significantly change in either acute or chronic users. Principle metabolites often have longer half-lives as well as different physical properties. For example, cocaine base easily crosses the blood-brain barrier, but benzoylecgonine does not. Thus, high brain concentrations of cocaine but low or absent metabolite levels argues for a recent drug exposure, while the presence of benzoylecgonine but no parent compound reasons for the passage of time and/or chronic use. The rate of conversion is partly dependent upon blood cholinesterase concentrations, which explains why the half-life of cocaine in newborns is hours longer than in adults. However, since cocaine toxicity is not dose-related (concentration measurements in individuals dying of cocaine toxicity totally overlap concentration in trauma patients where the presence of cocaine is an incidental finding), toxicity should never be attributed to cholinesterase deficiency.

The toxic effect of the metabolites is not yet resolved. Most have half-lives that are longer than cocaine and some are known to be physiologically active. Cocaethylene forms in small amounts only when alcohol and cocaine are present in the blood simultaneously.[9] Norcocaine is also an active metabolite. The toxic effects are believed to be significant, but so far no controlled studies describe its contribution to the cause of death.[7,8]

A recent study reviewed the toxicology findings in a large group of cocaine users who presented for treatment at an inner city emergency room.[9,10] Not only were the patients examined, but also cocaine and all the principal metabolites, including norcocaine, were measured simultaneously. Perhaps the most striking observation was that clinical toxicity did not relate to the measured blood concentrations. The same observation was made some years ago regarding post mortem cocaine concentrations when it became apparent that there was a complete overlap in blood concentrations between those dying of cocaine toxicity and those in whom cocaine was an incidental finding.[3]

In a series of emergency room patients, the individual with the highest blood concentration, 3.9 mg/l, a concentration that had in the past been considered close to fatal, had few symptoms and was discharged to police custody. Conversely, one of the few patients who died had a plasma concentration of 0.029 mg/l, a concentration below what is needed to produce measurable changes in pulse or blood pressure in humans. Concentrations in a second decedent were thirteen times greater (0.387 mg/l).[10]

The explanation for this phenomenon has actually been known for some time: except for the occasional "body packer" or "body stuffer" who is exposed to massive quantities of cocaine, the only cocaine users likely to get sick are the chronic users. The best way to determine which decedents were chronic abusers is to do a thorough investigation and examination to uncover the symptoms and anatomic alterations known to be associated with chronic cocaine use. Isolated measurements of blood or tissue concentrations alone simply do not provide sufficient information to make an informed interpretation. Analysis of hair or nails documents chronic use, but does not allow interpretation of route of administration or the dose consumed.

A number of studies, as well as an increasing wealth of practical experience by medical examiners around the world, has established no realistic absolute correlation between cocaine blood or plasma levels and stimulant intoxication, agitated delirium or death. In fact, cases of agitated delirium are often associated with low blood levels of cocaine. The effects of cocaine on the sodium and potassium channels of the heart appears to be related to dose and genotypic variability.[11]

NEUROCHEMICAL PATHOLOGY OF COCAINE DELIRIUM

The mesolimbic dopaminergic (DA) system plays a primary role in mediating the euphoric and rewarding effects of most abused drugs. Chronic cocaine use is associated with an increase in DA neurotransmission resulting from the blockade of dopamine uptake and mediated by the activation of dopamine receptors. Cocaine mediates its powerful reinforcement by binding to specific recognition sites on the DA transporter. DA transporters function to rapidly control the removal of transmitter molecules from the synaptic cleft. Using ligand binding and autoradiographic methods, 3 different neurochemical abnormalities have been consistently identified in the striatum of cocaine abusers dying of agitated delirium. Some of the abnormalities in the DA system involve alterations in DA receptors and in cocaine's ability to block the reuptake carrier by which DA is recycled back into the presynaptic nerve terminal. These neurochemical markers distinguish agitated delirium cases from nonagitated, nonpsychotic, sudden, cocaine-related deaths.

CONCLUSION

There appears to be a significant difference between agitated cocaine abusers who die and the nonagitated, nonpsychotic, sudden, cocaine-related deaths. Some evidence supports a genetic predilection for toxic susceptibility to cocaine's thermoregulatory defect. Cocaine is able to block the reuptake pump by which dopamine is recycled back to the nerve terminal.[12] It is also known that chronic cocaine abuse leads to a decrease in the density of the D1 receptors in the striatum, which may, in part, explain the escalating tolerance often seen in users. Striatal D2 receptors in nonpsychotic cocaine abusers are unchanged.[6] However, in the psychotic subgroup, a marked reduction in the numbers of receptors is found within the temperature regulatory centers of the hypothalamus.[6] There is increasing documentation that cocaine

induced channelopathies are significant factors in the induction of sudden cardiac death.[13]

Laboratory analyses are done to confirm the levels of the DA transporter in striatal regions. The DA transporter is the primary recognition site in the brain for cocaine. The analysis of DA transporter assays give highly consistent results and demonstrates a defect in the regulation of the DA transporter in cases of cocaine agitated delirium. The post mortem neurochemical analysis gives a neurochemical pathology measure of the density and affinity binding parameters in the putamen and nucleus accumbens by using a selective radioligand under standardized assay conditions. Reference control brain specimens are included with each radioligand binding assay and values are expressed in units of pmol/mg tissue.[5,12]

The results give values that are very well correlated with the reference values determined for a large cohort of agitated cocaine delirium cases first evaluated in Metropolitan Dade County, Florida. The assay values are provided for each case to the medical examiner with reference parameters for comparison with age-matched and drug-free control subjects and nonagitated, nonpsychotic, cocaine-related death victims. Additional assays may be conducted with other neuroreceptor markers, if warranted, to confirm and extend these results. These assays would include analyses of DA receptor subtypes in the hypothalamus and kappa opioid receptors in the amygdala, and functional DA uptake.

Knowing if cocaine is likely a significant issue in the death investigation during the initial investigation makes it easier to determine the steps to take during the autopsy and laboratory testing. In cases of agitated behavior and sudden death, it is prudent to collect the appropriate samples. Having collected the samples, the decision to test them or not can be made at a later time, as long as they are properly stored.

If the death is considered a "high profile" death and a grossly visible cause of death is found during the dissection, then the question of cocaine's contribution to the death becomes the issue. That answer becomes possible when the proper samples are available for analysis. Collecting the samples is not necessary in every death investigation, nor even in every suspected cocaine related death. But, without the appropriate samples being available for testing immediately or at a later time, the factual basis for a scientific or medical opinion is lacking.

SUMMARY

1. Scene and history often contain important information for an understanding of the cause of death.

2. In many regions, cocaine is often consumed with alcohol or other drugs.

3. In cases where agitated delirium is considered, a core temperature is taken as close as possible to the time of death. Hyperthermia, with core temperatures >103°F (41°C), supports reduced D2 receptors in the temperature regulatory centers of the hypothalamus. Survival on a respirator will likely lead to the development of rhabdomyolysis and sequela. Agitated delirium is more common and may be limited to chronic users who have recently used heavily and then have stopped consuming the drug. Drug levels may be absent or low at the time of the unusual behavior.

4. Drug analysis looks for the parent compound and the major metabolites.

5. Blood, serum and urine levels of cocaine do not uniformly correlate to toxicity.

6. Urine levels of cocaine and benzoylecgonine do not necessarily correlate to intoxication, so impairment cannot be determined solely based upon urine levels.

7. Caution is used when attempting to estimate time of ingestion, since more than one exposure may result in overlapping drug levels. Excretion half-life may vary to some limited extent from individual to individual.

8. Toxicologic analysis is performed on peripheral blood specimens whenever possible. Brain can be an extremely important sample for toxicological analysis. Compounds that cannot cross the blood-brain barrier, or cross it very poorly, were therefore formed in the brain. More than any other specimen, this sample represents the pharmacological effect upon the brain. With resuscitation, it may also represent a semi-sequestered sample that more accurately reflects the toxicology at the time of interest. Specimens other than blood may also yield important results.

9. When brain is prepared for analysis, coronal slices of the anterior striatum and the substantia nigra are collected as closely as possible to the time of death. The brain is sectioned through the corpus callosum in the sagittal plane, prepared as described above, and one-half of the brain frozen at as low a temperature as reasonably possible. Dry ice is used for shipment to a laboratory capable of doing the neurochemical analysis.

10. One of the principal target organs for cocaine toxicity is the heart.

11. Cocaine is known, and can be shown, to produce coronary artery spasm.

12. Histology may demonstrate atherosclerosis, focal myonecrosis, myofibrosis, and small vessel wall thickening. Cross-band necrosis is common.

13. Hair analysis can support a determination of acute or chronic drug use.

14. In determining whether cocaine is the cause of death, careful attention is paid to the circumstances and forensic findings. The drug may be directly or indirectly responsible for the death.

15. Other pathology always is considered before making a decision that cocaine is the cause of death.[14]

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