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<th>Query / remark</th>
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<tbody>
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Chapter 6

Cocaine Postmortem Distribution in Brain

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SUMMARY POINTS

- This chapter shows cocaine toxicokinetic and toxicodynamic aspects, postmortem distribution in brain, and comparisons with other specimens.
- Tolerance in chronic use is a confounding variable in cocaine-related deaths because high cocaine concentrations can be found without having been an overdose.
- Brain shows lower postmortem redistribution than blood.
- While blood is the most reported specimen to quantification of cocaine and determine the cause and manner of death, brain cocaine concentrations are close or equal to perimortem concentrations.
- Incidental deaths can be interpreted as cocaine-related death when cocaine influenced indirectly the lethal result.
- Brain is inside an isolated compartment with low enzymatic active and is less susceptible to postmortem redistribution.
- The possibility of relating the brain cocaine levels with neurobehavioral effects makes this specimen very attractive in forensic pathology.
- Brain tissue sampling can reveal information on the acute or chronic use and recent exposure can be determined by the cocaine/benzoylecgonine ratio.

KEY FACTS

- Due to the criminalization of use cocaine is often related to violent deaths.
- Cocaine-related deaths involve overdose, cardiovascular complications, violent situations, or unexpected behavior.
- Differences in response, tolerance, sensitization, and postmortem redistribution make it difficult to clarify the drug role in death.
- Once in the blood, cocaine is hydrolyzed by esterases to many inactive compounds, the enzyme activity continues after death, complicating the interpretation of drug levels in cadaveric blood.
- Vitreous humor and brain tissue are useful specimens to explain cocaine-related deaths.
- After consumption cocaine is rapidly distributed to the brain, which is impermeable to their inactive metabolites.

LIST OF ABBREVIATIONS

- AME anhydroecgonine methyl ester
- CNS central nervous system
- eNOS nitric-oxide synthase
- HB heart blood
- NO nitric oxide
- PB peripheral blood
- PMR postmortem redistribution
- VD volume of distribution

6.1 INTRODUCTION

Cocaine is an alkaloid found in coca plant of genus
Erythroxylum culturally used by native people in the Andean region for the vasoconstrictor action that improves breathing in high-altitude areas and the stimulant effects on the central nervous system (CNS). Chemically cocaine is a weak base with pKa = 8.6 at 15°C and molecular weight = 303.35 g/mol (O’Neil, 2006). An average of 400 kg of coca leaves are used to produce 1 kg of coca paste and 0.5 kg of cocaine hydrochloride (UNODC, 2015). Dried coca leaves are moistened with alkaline solution to solubilize cocaine in kerosene (or other liposoluble solvent, such as, gasoline or diesel) and the solution is then mixed with dilute sulfuric acid to convert soluble alkaloids into an aqueous acid solution. Ammonia water is added to the sulfuric acid solution and cocaine sulfate is converted to a
free-base form that is filtered and termed coca paste (Fig. 6.1). Cocaine base is a purer form obtained from purification of coca paste by sulfuric acid and an oxidant agent (Fukushima et al., 2014). Both are free-base forms and can be smoked, unlike esters forms (hydrochloride or sulfate) obtained from purification and crystallization of cocaine base that have a higher melting point (98°C) and are used by the intranasal or intravenous route.

Crack cocaine is a name that has emerged in the United States to describe smoked cocaine obtained from the conversion of cocaine salts in free-base form by the addition of alkaline solution and heating. However, depending on the geographic region smoked cocaine has different compositions, in Brazil and Colombia smoked cocaine refers mainly to coca paste that contains petroleum residues and shows high neurotoxicity.

While correlating drug blood levels with administered dose and its effects is a common task in clinical pharmacology, understanding toxicological effects of illegal drugs is a challenge because the purity and composition are varied and information about the use conditions (frequency and consumption of other drugs) is not always available. Cocaine effects in eventual and chronic users may differ greatly and are strongly influenced by interindividual differences, drug tolerance, and sensitization. Since blood cocaine level interpretation is a difficult task in living individuals, in postmortem cases it is more complex due to the process of postmortem drug redistribution and actual blood levels do not necessarily prove or disprove the presence of a direct cocaine effect (García-Repetto, Soria, Gimenéz, & Jurado, 2008; Stephens, Jentzen, Karch, Mash, & Wettl, 2004). Because cocaine acts on the CNS, brain specimens are useful to determine the role of cocaine in the cause of death. Brain is inside an isolated compartment, shows low enzymatic activity resulting in slower cocaine degradation, the blood–brain barrier is not permeable to polar cocaine metabolites and cocaine and its main metabolite benzoylecgonine levels in the brain are closer to perimortem concentrations (Carvalho et al., 2013; Spiehler & Reed, 1985; Stimpfl & Reichel, 2007). Thus, this chapter shows cocaine toxicokinetic and toxicodynamic aspects, postmortem distribution in brain, and the comparison with other specimens and advantages and limitations of brain use to clarify cocaine-related deaths.

6.2 TOXICOKINETICS AND TOXICODYNAMICS OF COCAINE

Cocaine effects depend on toxicokinetic and toxicodynamic processes that occur simultaneously.

After intravenous administration, cocaine is rapidly distributed to the CNS and is also distributed to peripheral organs in velocity order to the heart > kidney > adrenal gland > liver (Fowler, Volkow, Wang, Gatley, & Logan, 2001).

In the intranasal route, bioavailability ranges between 49% and 94% with a low absorption rate. Plasma levels, although smaller, are maintained for a longer period due to slower rate of absorption, the peak plasma concentration occurs on average after 30 minutes and is subject to differences in the effectiveness of aspiration technique (partial swallowing of the dose) and the individual characteristics of the user. Doses of about 0.4 mg/kg body weight (about 30–40 mg) are associated with a peak plasma concentration of 50 ng/mL, while those corresponding to 1–2 mg/kg are associated with 100–200 ng/mL (Barnett, Hawks, & Resnick, 1981; Cone, 1995, 1998). Plasma average concentrations around 350 ng/mL were observed 14 minutes after a second dose of 1.37 mg/kg of cocaine hydrochloride was administered by intranasally 40 minutes after the first dose to chronic users (Foltin & Haney, 2004).

In the metabolism (Fig. 6.2) cocaine is biotransformed to benzoylecgonine (c. 45%), ecygmine methyl ester (c. 40%), and others, such as norcocaine and ecgonine (Brzezinski, Abraham, Stone, Dean, & Bosron, 1994; Carmona et al., 1996; Mets, Diaz, Soo, & Jamdar, 1999). In liver cocaine is converted to norcocaine, which is also distributed to the brain, is pharmacologically active, and is a hepatotoxin (Fowler et al., 2001; Mets et al., 1999).Whatever the administration route, when cocaine is consumed with ethanol, cocaethylene is produced by a transesterification reaction and catalyzed by carboxylesterases that are formed concomitantly with benzoylecgonine, but at ethanol high concentration (100 mM) the transesterification rate is 3.5 times faster than the hydrolysis (Brzezinski et al., 1994).

Cocaine shows volume of distribution (VD) between 1.2 and 1.9 L/kg (Barnett et al., 1981) and the plasmatic
Cocaine distribution in brain

**FIGURE 6.2** Cocaine metabolism. Biotransformation, burning, and transesterification of cocaine.

Cocaine elimination half-life depends on the administration route, the intravenous route has a half-life between 2.4 and 5.8 hours, the pulmonary route between 2.7 and 6.3 hours, and the intranasal route between 2.7 and 7.3 hours (Cone, 1998). The very rapid and intense effect of smoking cocaine is justified by the high vascularity of pulmonary alveoli and proximity to the heart and brain (Schwartz, Luxenberg, & Hoffmann, 1991). The chemical availability of smoked cocaine is about 70%, but depends on the vaporizing temperature, the pipe, and user experience of puffing (Cone, Hillsgrove, & Darwin, 1994; Cone, 1995; Jacob, Ewis, Elias-Baker, & Jones, 1990; Nakahara & Ishigami, 1991; Neudorfl, Hume, Pilon, & Lawrence, 1997; Shimomura, Hodge, & Paul, 2001). When crack cocaine is smoked the burning compound anhydroecgonine methyl ester (AME) is also absorbed with cocaine and its biotransformation is similar to cocaine (Fig. 6.3) (Fandiño, Toennes, & Kauer, 2002).

Cocaine is a potent local anesthetic, vasoconstrictor, and CNS stimulant. The recreational use is based on the action in dopaminergic, noradrenergic, and serotoninergic pathways (Erzouki, Allen, Newman, Goldberg, & Schindler, 1995; Volkow et al., 2006). The feeling of euphoria and pleasure is mainly attributed to blocking dopamine transporters with an increase in the extracellular dopamine concentration which acts on D1 and D2 receptors (Carboli et al., 2001; Heien et al., 2005; Hows, Lacroix, Heidbreder, Organ, & Shah, 2004; Ritz, Lamb, Goldberg, & Kuhar, 1987). Dopamine receptors are distributed in regions clustered into high (putamen > accumbens > caudate), moderate (thalamus > prefrontal > posterior cingulate gyrus > amygdala, hippocampus and temporal pole), and low (orbital cortex, precentral gyrus, and cerebellum) receptor density (Fowler et al., 2001). The cocaine lethality is often associated with cardio- toxic effects. Cocaine is rapidly distributed to cardiac tissue (Fowler et al., 2001) and it seems that there is a synergic effect between sympathomimetic and anesthetic action, the inhibition of sodium influx into cardiac cells impairs the conduction of nerve impulses, creating an ideal situation for the action of norepinephrine in generating tachycardia and eventually ventricular fibrillation. The adrenergic central stimulation of the hypothalamus and medulla causes peripheral vascular constriction and subsequently elevated blood pressure and increased heart rate. The cardiotoxic effects have also originated from the inhibition of muscarinic receptors in brain and cardiac tissue (Flynn, Vaishnav, & Mash, 1992; Miao, Qui, & Morgan, 1996; Sharkey, Ritz, Schenden, Hanson, & Kuhar, 1988; Shannon, Stambler, Komamura, Ibara, & vatner, 1993) and by a decrease in NO production, a substance involved in vasodilatation of coronary arteries. The acutely coronary vasospasm and decrease in nitric-oxide synthase (eNOS) by downregulation result in progression of...
coronary artery diseases (He, Yang, & Zhang, 2005). The cocaine sympathomimetic action results in hypertension and reduction of blood flow in the coronary circulation that increases the risk of ventricular arrhythmia, ischemia, and acute myocardial infarction (He et al., 2005; Kiyatkin & Brown, 2005; Vongpatanasin, Mansour, Chavoshan, Arbique, & Victor, 1999).

While the cocaine action mechanism has been described, the mechanism of action of the pyrolysis product EMA produced in smoked cocaine is not fully understood. It has been shown that EMA exerted a negative inotropic effect on isolated ferret and human myocardium (Woolf, Huang, Ishiguro, & Morgan, 1997), acted on M2 cholinergic receptors in the heart to produce cardiac toxicity (Huang, Woolf, Ishiguro, & Morgan, 1997), and the hypotension results in tachycardia, probably due to baroreceptor compensation to decrease mean arterial pressure (Scheidweiler, Shojai, Plessinger, Wood, & Kwong, 2000). The cardiovascular effects of cocaine combined with EMA can result in more serious cardiovascular complications when cocaine is smoked. Thus, identifying smoked cocaine use may be important in clarifying the cause and manner of death.

6.3 COCAINE POSTMORTEM REDISTRIBUTION AND BRAIN CONCENTRATIONS

Although cocaine is a common toxic agent in forensic cases, interpreting its role in deaths is a challenge for forensic pathologists. The diagnostic criteria for a death from acute cocaine intoxication include a review of the police investigation, autopsy, and identification and quantification of cocaine and its metabolites in the blood and other biological specimens (Stephens et al., 2004). In addition, the pathologists should interpret cocaine concentrations in accordance with the postmortem redistribution (PMR) phenomena.

The PMR refers to changes in drug concentrations that occur between the time of death and the collection of the biological samples at autopsy. Drug properties such as VD, lipophilicity, and pKa affect PMR; basic and lipophilic drugs with high VD are particularly susceptible. Although drugs with VD greater than 3 L/kg have a high potential to PMR, the VD is affected by age, gender, disease, and body composition and PMR is also affected by the position of the body after death and subsequent

![Smoked cocaine metabolism. Biotransformation and transesterification of smoked cocaine.](image-url)
movement of the body by law enforcement and medical personnel (Leikin & Watson, 2003; Péléissier-Alicot, Gaulier, Champsaur, & Marquet, 2003; Yarema & Becker, 2005). After cell death, basic and lipophilic drugs at high concentrations in cells are redistributed to extracellular space, increasing its concentration in the blood (Péléissier-Alicot et al., 2003). Cocaine binds to the myocardium and can be released into the heart blood (HB) after death in concentrations greater than those found in peripheral blood (PB) (Yarema & Becker, 2005). The diffusion from the lungs and the liver can also increase cocaine concentrations in HB (Stephens et al., 2004) and in smoke cocaine it is theoretically expected to increase cocaine concentrations in HB by diffusion from the lungs. On the other hand, if PMR is affected by the position and movement of the body after death and by the body’s physical state it is expected that the PB will not always be the most suitable matrix. Higher cocaine and benzoylecgonine levels were found in femoral venous blood (cocaine = 3.21 µg/mL and benzoylecgonine = 19.85 µg/mL) than in right cardiac blood (cocaine = 1.11 µg/mL and benzoylecgonine = 3.46 µg/mL) (Alvear, von Baer, Mardones, & Hitchens, 2014). Further, there will be situations in which PB collection is not possible, such as, when femoral vessels are injured (Carvalho et al., 2013). Whatever the location of the blood collection, the residual esterases activity decreases the cocaine concentrations in blood by hydrolysis after death and it is recommended to collect two separate blood samples and store these mixed with sodium fluoride at a final concentration of between 5 and 10 mg/mL, acidified and frozen. The site and sample handling should be documented (Carvalho et al., 2013; Stephens et al., 2004).

For postmortem forensic toxicology analysis, the Forensic Toxicology Laboratory Guidelines (SOTF/AAFS, 2006) suggest collection of brain (50 g), liver (50 g), kidney (50 g), HB (25 mL), PB (10 mL), and the total available quantity of vitreous humor, bile, urine, and gastric contents. Although all samples can be used for cocaine and its metabolites quantification, the most common are blood and urine. While urine is often used to determine cocaine consumption by screening tests and it is easy to prepare for chromatographic analysis, blood is the most reported specimen for cocaine quantification and to determine the cause and manner of death. The cocaine and benzoylecgonine concentrations determined in blood and other postmortem specimens are shown in Table 6.1.

Vitreous humor is a useful specimen for cocaine analyses because it is easy to collect and the preparation is fast and simple. The collection may be performed in both eyes by introducing a needle (volume of 20 mL with 0.8 mm diameter and 25 mm length) in sclera at an angle of 45 degrees in relation to the syringe axis. Generally about 5 mL of vitreous humor are collected from both eyes and due to the pH being about 7.8 it is recommended to adjust the pH to 6.0 to prevent cocaine hydrolysis before storage. Although cocaine concentrations tend to increase, the greater the postmortem interval because of dehydration of the vitreous chamber, vitreous humor is less susceptible to PMR and has been shown to be more adequate in identifying cocaine use than whole blood. In overdose cases the cocaine concentrations in vitreous humor showed strong correlation with HB and a strong correlation between vitreous humor/brain and HB/brain was shown (Carvalho et al., 2013).

Brain is the most interesting matrix to analyze psychoactive drugs because it represents the local action of the drug and shows higher drug concentrations than blood. Cocaine metabolism in the brain is much lower than in blood and only lipophilic compounds such as norcocaine and cocaethylene are distributed to the brain, both are pharmacologically active and showed a higher uptake and slower clearance from brain than cocaine itself due to their higher lipophilicity (Brzezinski et al., 1994; Fowler et al., 2001). The possibility of relating the cocaine content in the brain with the neurobehavioral effects makes this specimen very attractive in forensic pathology.

After intravenous administration, cocaine is rapidly distributed to CNS with maximal uptake occurring in the striatum located in the basal ganglia, the brain region containing the highest density of dopamine terminals. Cocaine distribution to the cerebellum (a region devoid of dopamine transporters) is also rapid, but clearance is lower than in the striatum, the ratio of striatum to cerebellum is approximately 2:15 minutes. Half-times for clearance from peak were striatum > thalamus > precuneus > cerebellum, in the striatum the clearance half-time was about 20 minutes (Fowler et al., 2001).

The brain shows high availability, weighing about 1000 g, and no more than 10 g is typically needed in the analytical procedure. On the other hand, it is a complex matrix that requires many laborious steps in sample preparation for chromatographic analysis. The brain is removed and sectioned into coronal slices and basal ganglia can be collected, homogenized, and frozen at pH 6.0. However, it was shown that a homogeneous distribution of cocaine and benzoylecgonine in basal ganglia, cerebellum, and frontal cortex (Carvalho et al., 2013), the basal ganglia is recommended to collect especially as it is of interest in neurochemical analyses (Stephens et al., 2004).

Brain shows low metabolic activity, resulting in slower cocaine degradation; the main metabolite benzoylecgonine is polar and does not cross the blood–brain barrier, it is inside an isolated compartment, where the drug concentrations measured are close to or equal to perimortem concentrations (Bertol, Trignano, Di Melia, Di Padua, & Mari, 2008; Carvalho et al., 2013; Spiehler & Reed, 1985;
Stimpfl & Reichel, 2007). Benzoylecgonine found in the brain was formed in the brain and the enzymatic hydrolysis of cocaine evaluated in rat brain tissues corresponds to 1.3 ± 0.12% relative to blood (Gao et al., 2008). 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 neurobehavior and death. High brain cocaine concentrations but low or absent metabolite levels indicate recent exposure, while the presence of benzoylecgonine but no parent compound establishes the passage of time or suggests chronicity of use (Stephens et al., 2004). Therefore, the concentrations in brain tissue are useful in estimating the disposition of cocaine and benzoylecgonine at collection time and consequently with the time of death since the PMR, although it occurs, is time-dependent and the relationship (ratio) is maintained. The cocaine/benzoylecgonine ratios have special interest to give an idea about the interval between cocaine consumption and death and may be indicative of overdose if the cocaine/benzoylecgonine ratio is higher than 1. In overdose cases were showed higher cocaine/benzoylecgonine ratios in brain and the cocaine mean concentrations were higher in brain than blood (Bertol et al., 2008; Carvalho et al., 2013; Spiehler & Reed, 1985).

### TABLE 6.1 Cocaine and Benzoylecgonine Concentrations in Cadaveric Specimens

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Blood (µg/mL)</th>
<th>Vitreous Humor (µg/mL)</th>
<th>Brain (µg/g)</th>
<th>Urine (µg/mL)</th>
<th>Sampling</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>COC</td>
<td>BE</td>
<td>COC</td>
<td>BE</td>
<td>COC</td>
</tr>
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<td>Peretti et al. (1990)</td>
<td>330.00</td>
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<td>NA</td>
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<tr>
<td>Patel (1996)</td>
<td>104.00</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Jenkins et al. (1999)</td>
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<td>0.024–9.10</td>
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<td>0.0–0.01</td>
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<td>0.00–1.40</td>
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<td>Tineschi et al. (2002)</td>
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<td>86.10</td>
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<td>NA</td>
<td>99.10</td>
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<td>Lewis et al. (2003)</td>
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<td>Darke et al. (2005)</td>
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<td>0.00–20.00</td>
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<td>Paul et al. (2005)</td>
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<td>0.09–2.61</td>
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<td>Takekawa (2005)</td>
<td>19.40</td>
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<td>NA</td>
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<td>Garcia-Repetto et al. (2008)</td>
<td>0.02–7.24</td>
<td>0.01–140.40</td>
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<td>Mash et al. (2009)</td>
<td>2.56–4.04</td>
<td>3.53–4.47</td>
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<td>0–24.43</td>
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<td>0.21–5.91</td>
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<td>Alvear et al. (2014)</td>
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<td>3.46</td>
<td>0.23</td>
<td>2.63</td>
<td>2.38</td>
</tr>
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</table>

*Heart blood.
*Basal ganglia.
*Nucleus accumbens.
COC, cocaine; BE, benzoylecgonine; NA, not analyzed.
Note: Concentrations refer to range if sampling was > 1.
The comparison of different specimens seems to be the most appropriate to interpret the death circumstances. Carvalho et al. (2013) compared two cocaine-related deaths: in the first case the drug concentrations in brain basal ganglia (cocaine = 0.26 µg/g and benzoylecgonine was not detected) and vitreous humor (cocaine = 0.12 µg/mL and benzoylecgonine = 0.21 µg/mL) were low, but the circumstances, autopsy, and cocaine concentrations in HB suggest a classical overdose with cocaine/benzoylecgonine ratio > 1 (cocaine = 1.04 µg/mL and benzoylecgonine = 0.63 µg/mL), and in the second case, although the cocaine concentrations in HB (cocaine = 1.62 µg/mL and benzoylecgonine = 4.43 µg/mL) suggested a classical overdose and other specimens have higher analyte levels (cocaine = 2.43 µg/g and benzoylecgonine = 1.60 µg/g in brain basal ganglia; cocaine = 1.26 µg/mL and benzoylecgonine = 3.19 µg/mL in vitreous humor), the cocaine/benzoylecgonine ratios were < 1 for both HB and vitreous humor and the cause of death was polytrauma as a result of having been hit by a vehicle. In many incidental cases 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, e.g., with cocaine being the reason for the person being subjected to that trauma (e.g., an agitated delirium person running in front of a car). These deaths are typically listed as accidental or homicidal in manner, depending upon the circumstances associated with the investigation. They do not usually meet the requirements to be designated as suicidal (Stephens et al., 2004). Due to the cocaine action on the neurotransmission, neurochemical analyses can complement the interpretation of drug levels in specimens. In cocaine consumers it was referred increased dopamine transporter binding sites (Little et al., 1998) but decreased dopamine transporter levels was related in individuals whose death was related to excited delirium (Mash et al., 2009). Equal to what happens with benzoylecgonine, cathecolamine and indoleamine concentrations are directly related to alterations in the brain because polar molecules do not cross the blood–brain barrier. In cases of suspected agitated delirium one cerebral hemisphere is coronally sectioned into 1-cm thick slices and should be collected from structures with a high density of dopamine receptors, such as the substantia nigra and striatum. For neurochemical analyses the brain samples should be collected in the first 24 hours, ideally less than 12 hours from the time of death to minimize the effects of autolysis. The brain slices are rinsed with physiologic saline, placed on a plastic sheet, and flash frozen with liquid nitrogen or on dry ice. The samples can be stored in a −70°C freezer until the neurochemical analysis (Stephens et al., 2004). As cocaine enhances dopamine by inhibiting the clearance of extracellular dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and homovanillic acid can be quantified in striatum.

**MINI-DICTIONARY OF TERMS**

- **Blood–brain barrier**: Dynamic barrier that separates the brain from the circulatory system.
- **Chromatographic analysis**: The most common technique applied in toxicological analyses to confirm and to quantify drugs in biological samples.
- **Excited delirium Syndrome**: Symptomimetic syndrome characterized by delirium and agitation, combative, unexpected strength, and elevated body temperature.
- **Biological half-life**: Toxicokinetic property described as the time required to eliminate half of an administered dose.
- **Neurochemistry analysis**: Quantification of neurotransmitters or related parameters in brain.
- **pKa**: Negative decadic logarithm of the ionization constant. The pKa of a weak electrolyte is the pH at which it is 50% dissociated. The dissociated form is more hydrosoluble and the nondissociated (molecular) form is more liposoluble. For weak base, pH values above the pKa shifts the equilibrium to the molecular form.
- **Postmortem redistribution (PMR)**: Changes in drug levels in different compartments over time after death which hinders the comparison with clinical levels.
- **Screening tests**: Presumptive test applied to biological specimens which aims to exclude samples with low probability of positivity and thus reduce the number of unnecessary confirmatory analyses.
- **Sensitization**: Phenomenon characterized by an increase in response to cocaine.
- **Tolerance**: Neuroadaptation characterized by progressive increase in the dose consumed to obtain the same sensations as experienced with the initial dose.
- **Toxicokinetic**: Drug kinetic in the body composed by absorption, distribution, metabolism, and excretion.
- **Toxicodynamic**: Mechanism of toxicity determined by drug interaction with receptors.
- **Volume of distribution**: Toxicokinetic property described as the hypothetical volume of body fluid that would be required to dissolve the total amount of drug.

**REFERENCES**


PART | I General Aspects, Features of Ill Health and Setting the Scene


Abstract
Cocaine is frequently related to deaths as a result of overdose, cardiovascular complications, psychiatric disorders, or violent situations associated with criminalization of consumption. Differences in drug response, tolerance, and sensitization, plus postmortem redistribution hinder the elucidation of cocaine-related deaths. Acute poisoning is easily verified when the blood concentration is very high, such as, in body packers cases, but in most death cases to interpret blood levels is challenging. Brain is a very interesting specimen because it is inside an isolated compartment with low enzymatic activity, most cocaine metabolites do not cross the blood—brain barrier and take longer periods of time to occur due to putrefactive processes. Understanding the drug distribution in brain and its correlation with blood levels and other specimens helps to interpret the role of cocaine in death. This chapter shows cocaine toxicokinetic and toxicodynamic properties and postmortem distribution in brain and other specimens.

Keywords: Postmortem; redistribution; brain; blood; vitreous humor; cocaine