Cocaine

23

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Abstract

Cocaine is one of the most popular drugs of abuse and is considered to be the most abused major stimulant in the United States. It is classified by the Drug Enforcement Administration as a Schedule 2 drug because it may be used medicinally as a topical local anesthetic. Unlike other local anesthetics, cocaine has additional actions, including its ability to block reuptake of the neurotransmitters norepinephrine, dopamine (DA), and serotonin (5-HT). Norepinephrine is responsible for the classic adrenergic effects seen with cocaine use, while the desirable effects are mediated primarily by DA. Cocaine is well absorbed by intravenous, intranasal, and smoking routes of administration, but the time course and extent of absorption differ among them. Cocaine contains two ester moieties that are hydrolyzed in vitro and in vivo. The alkyl ester of cocaine is hydrolyzed to benzoylecgonine via spontaneous hydrolysis as well as liver methylesterases, and the phenyl ester is hydrolyzed to ecgonine methyl ester by plasma cholinesterase and liver benzoylesterases. Combined use of ethanol and cocaine causes the production of cocaethylene. Cocaine use can produce impairment consistent with its pharmacologic effects. Cocaine can also account for death by a number of mechanisms, including excited delirium, cardiac arrhythmias, and overstimulation of the central nervous system.

Keywords

Cocaine · Toxicology · Pharmacology · Analysis · Interpretation

Introduction

History

Cocaine is an alkaloid found in *Erythroxylum coca*, which grows principally in the northern South American Andes. The plant favors higher elevations (up to 6000 feet) because at lower elevations (below 1500 feet), the alkaloid content is significantly diminished because of more rapid growth. Coca leaves may be harvested about 2 years after planting. Then, depending on the altitude, the leaves may be harvested up to three times a year. The leaves are dried and converted into a coca paste made by macerating coca leaves in an organic solvent and sulfuric acid. Further treatment of coca paste with hydrochloric acid

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yields cocaine hydrochloride. The yield from 100 kg of coca leaves is about 1 kg of coca paste or 800 g of cocaine hydrochloride.

Cocaine is a psychotropic drug that has been used for 2000 years. The Incas of Peru chewed the leaves of the coca plant in their religious ceremonies. Later, during the Spanish conquest, the Spaniards found that the Peruvian Indians could not perform their heavy labor in the mines when deprived of the plant. Today, coca leaves (containing about 0.7% to 1.5% of total alkaloids) are still used by the indigenous populations of the high Andes, who chew them mixed with lime to cope with the rigors of life at high altitude.

In the mid-nineteenth century, Carl Wöhler, the chemist who synthesized urea, had coca leaves imported to Germany and presented them to his graduate student, Albert Niemann, to analyze. Niemann was the first to successfully isolate cocaine from the coca plant. From the 1860s through the turn of the century, cocaine appeared in various elixirs and tonics purported to have "magic" properties. Some of the more famous preparations included Vin Mariani, a mixture of wine and cocaine, and the original Coca-Cola® recipe developed by John Pemberton.

The Italian physician Paolo Mantegazza was the first to spark interest in the medicinal uses of cocaine. Several papers had been written in the 1870s about cocaine's potential use for treating morphine addiction, but not until Sigmund Freud popularized the drug in his famous 1884 treatise "Über Coca" did it become well known in the scientific community. In 1884, Carl Koller became the first physician to use cocaine as a topical anesthetic in ophthalmologic surgery. It was popularly reported to be a wonder drug that would satiate the hungry, give strength to the fatigued, and cause people to forget their misfortune.

Despite numerous early reports of cocaine toxicity, including cardiac arrhythmias and fatalities, cocaine-containing products became ever more popular. By 1903, the Coca-Cola Company agreed to use (solely as a flavoring agent) only coca leaves from which cocaine had been removed. In 1914, as cocaine abuse began to be viewed as a problem, the drug was labeled a narcotic (albeit incorrectly) under the Harrison Narcotic Act, and over-the-counter sales were discontinued. In 1970, under the Controlled Substances Act, cocaine was scheduled as a drug with some medicinal value but with a high potential for abuse (Schedule II). It continues to have some medical use, which is almost exclusively limited to topical administration as a local anesthetic in ear, nose, and throat surgery (as the hydrochloride salt in 10–20% solutions) and in ophthalmologic procedures (as a 1–4% solution). The usual maximum recommended dose for intranasal local anesthesia is 100–200 mg (1–2 mL of 10% solution). Older preparations of cocaine include tetracaine, adrenaline, and cocaine (TAC), a topical anesthetic solution used in suturing extremity wounds, in which cocaine was included because of its rapid onset of action. Topical adrenaline-and-cocaine gel is still sometimes used in pediatrics for anesthetizing children's lacerations. Cocaine is one of the most popular drugs of abuse and is considered to be the most abused major stimulant in the United States exceeding methamphetamine nationally, although the predominance of one drug over the other depends on regional differences. It has acquired numerous street names including bazooka, blow, coke, crack, dust, flake, gold dust, happy dust, lady, nose, nose candy, rock, snow, speedball (when mixed with heroin and injected), stardust, tick (when smoked with phencyclidine), toot, and white. In a 2016 National Survey on Drug Use and Health, it was reported that 14.4% of the surveyed US population between the age of 12 and 17 have used cocaine in their lifetimes, and 16.6% of those over the age of 26 used cocaine at least once. The greatest mention of lifetime use was for the 55–59 age group at 26.4% reflecting the popularity of the drug back in the 1980s and 1990s. Despite this, recent reports show that cocaine-related deaths in 2015 was the highest since 2006 according to the Substance Abuse and Mental Health Services Administration and first time use from 2013 to 2015 increased 61%. The increase in use has been correlated to the increase in cocaine trafficking and cultivation. Cocaine also is frequently seen in combinations with fentanyl and/or heroin in seized drug exhibits.

Cocaine is sold on the street in two forms: the hydrochloride salt and crack. The salt varies considerably in purity. It can be as low as 30%, but recently, exhibits have shown the purity to be much higher, in some cases exceeding 90% with greater than 80% typical. Historically, the salt form is typically diluted ("cut") with agents such as mannitol, lactose, and sucrose to add bulk. In addition, readily available central nervous system stimulants such as caffeine and ephedrine and other local anesthetics such as lidocaine, procaine, and benzocaine had been commonly used as diluents to simulate the actual drug. More recently, diphenhydramine and levamisole have been reported as cutting agents, the latter having been described widely in the literature to cause severe deleterious effects including agranulocytosis and vasculitis. The cocaine powder supplied by dealers is often clumpy and first needs to be chopped. This is usually done using a mirror and a razor blade. Then the cocaine is arranged into thin lines about 30–60 mm long and 2 mm wide (resulting in an average dose of 25 mg) and then snorted through a straw or "tooter." Alternatively, cocaine may be snorted from a "coke spoon" or "bullet" (a vial containing cocaine is inverted over a closed chamber and the chamber is rotated for convenient snorting). A single long fingernail may serve as a natural coke spoon. Alkaloidal cocaine base, known as *free base*, is made by dissolving cocaine hydrochloride salt in an aqueous alkaline solution and then extracting the free basic form with a solvent such as ether. "Crack" is a free base form of cocaine produced by using sodium bicarbonate to create the alkaline aqueous solution, the extract of which is then dried by heating (the name coming from the "crackling" sound made by the heated extract). After heating, the mixture is cooled and filtered, and the free-base cocaine precipitates into small pellets or "rocks." A typical "rock" weighs about 20 mg and costs US$5.00. These "rocks" can then be smoked in a crack pipe. Crack pipes range from elaborate glass pipes to a soda can with a hole. The heat generated from these pipes can be very high, and chronic crack users may show stigmata of thermal injuries on the fingers.

Chemistry

Cocaine (methylbenzoylecgonine), an ester of benzoic acid and the amino alcohol methylecgonine, which contains a tropine moiety, is chemically but not pharmacologically related to atropine. The ecgonine portion of the molecule has four chiral carbon atoms and can exist as four racemates (eight optically active isomers).

Cocaine is structurally different from other local anesthetics by virtue of its tropine moiety. However, like other local anesthetics, cocaine consists of a hydrophobic region and a hydrophilic region. The hydrophobic region contains a benzene ring, whereas the hydrophilic region consists of a secondary or tertiary amine. Cocaine is also similar to other local anesthetics in that it contains ester linkages which allow the body to hydrolyze and deactivate the drug. The ester group is also susceptible to in vitro hydrolysis.

Pharmacology

Effects and Toxicity

Cocaine is used medicinally as a topical local anesthetic. Clinically, its most important mechanism of action lies in its ability to block initiation and conduction of nerve impulses by decreasing axonal membrane permeability to sodium ions in fast sodium channels and thereby increase the threshold required to generate an action potential. Cocaine has additional actions, however, that make it unique among local anesthetics, including its ability to block reuptake of the neurotransmitters norepinephrine, dopamine (DA), and serotonin (5-HT). Norepinephrine is responsible for the classic adrenergic effects seen with cocaine use, including mydriasis, vasoconstriction, hypertension, and tachycardia. The desirable effects of cocaine, mediated primarily by DA, include intense euphoria, psychic energy, heightened sexual excitement, and self-confidence (elevation of mood). Potential undesirable effects include paranoia, hallucinations, and dysphoria.

After an acute dose of cocaine, brain concentrations of DA increase briefly and then decrease markedly to below normal concentrations, corresponding to the central stimulatory effects ("rush") and depression ("crash") that the cocaine user experiences. Cocaine prevents the reuptake of DA into the presynaptic dopaminergic neuron by binding to receptors on the DA transporter located on the dopaminergic nerve terminal. This DA reuptake, which is mediated by sodium, chloride, and energy-dependent active transport, is inhibited when cocaine binds to the sodium-binding site on the transporter and alters the chloride-binding site, thus preventing the binding of both ions. Because translocation of DA across the membrane of the presynaptic neuron is inhibited, increased extracellular DA concentrations chronically stimulate the DA receptor in the postsynaptic neuron.

For equivalent plasma cocaine concentrations and DA transporter blockade, smoked cocaine induces significantly greater self-reports of "high" than intranasal (IN) cocaine and shows a trend for a greater effect than intravenous (IV) cocaine. Such reports and the fact that the time to reach peak subjective effects is significantly faster for smoked cocaine (1.4 min) than for IV cocaine (3.1 min) and IN cocaine (14.6 min) demonstrate the importance of speed of cocaine delivery into the brain for its reinforcing effects.

Chronic cocaine administration alters the DA transporter in the mesolimbic regions of the brain. Increased densities in the DA transporter have been observed postmortem in the brains of cocaine abusers and in vivo in acutely abstinent cocaine users. Upregulation of cocaine-binding sites in the brain produces a need for additional cocaine to continue experiencing its rewarding effects. Chronic cocaine users repeatedly administer cocaine, increasing the synaptic levels of DA. This process becomes cyclical and demonstrates how a cocaine binge or "run" is followed by a crash and why the temptation to self-medicate is so strong.

Cocaine-excited delirium, which is associated with hyperthermia, delirium, agitation, cardiorespiratory arrest, and sudden death, may be due to an inability of the DA transporter to upregulate as it does in most chronic cocaine users. In these individuals, increased densities of DA receptors are not observed, and the lack of increased receptor sites has been postulated to produce insufficient DA reuptake, leading to excessive DA concentrations in the synapse. The extreme hyperthermia in these individuals may be related to the observed downregulation in DA-2 receptors in the hypothalamus, which are responsible for decreasing body temperature. DA-1 receptors, which are responsible for increasing the body temperature, are not affected. Individuals with a high body mass index appear to be at highest risk because they generate the most heat through skeletal muscle activity. Cocaine also binds to the 5-HT transporter and inhibits 5-HT reuptake. Acutely, 5-HT would be expected to partially antagonize the stimulatory effects of cocaine in the naive user (this expectation was the basis for investigating the use of 5-HT reuptake inhibitors for the treatment of cocaine dependence). Withdrawal from cocaine after chronic use produces a decrease in synaptic 5-HT concentrations by altering the function of the presynaptic 5-HT receptor that controls the amount of 5-HT available for release. Alterations in the sensitivity of postsynaptic receptors to 5-HT also occur. These alterations have been implicated in the depression and craving seen after cocaine withdrawal.

Repeated doses of cocaine have been shown to produce both diminished effects (tolerance) and increased effects (sensitization). Acute tolerance to cocaine typically occurs during a binge in which the users dose themselves repeatedly, leading to an acute depletion of DA and a diminished response. Sensitization tolerance, or reverse tolerance, typically occurs with chronic cocaine use and longer dosing intervals and does not appear to be related to brain catecholamine concentrations. Such observations support theories that sensitization to cocaine may occur via changes to receptors that make them more sensitive to cocaine or its action at other receptors.

The most common clinical manifestations following acute cocaine intoxication include profound central nervous system stimulation, with psychosis and repeated grand mal convulsions,

ventricular arrhythmias, respiratory dysfunction with Cheyne–Stokes breathing, and, ultimately, respiratory paralysis. Other symptoms include mydriasis, hypertension leading to hypotension, and small-muscle twitching. The ability of cocaine to cause increased muscular activity and vasoconstriction may produce extreme hyperthermia. The patient may also lapse into a coma.

Symptoms of chronic cocaine use, other than psychiatric disturbances, include rhinitis (with possible nasal septum perforation), shortness of breath, cold sweats, tremors, violent protective behavior, distorted perception, tachycardia, tachypnea, dyspnea, and hyperkinetic behavior. The drug can injure cerebral arteries, and an acute hypertensive episode following a single dose in a chronic user can cause cerebral vessels to rupture. Acute myocardial infarctions have occurred after even therapeutic doses of cocaine. Chronic cocaine use accelerates the development of atherosclerosis and can also cause aortic dissection, myocarditis, and cardiomyopathy which are frequent findings at autopsies in chronic cocaine abusers. Cardiovascular toxicity resulting from cocaine use may be related to individual sensitivity and therefore may not be predictable on the basis of dose, route of administration, or underlying heart disease.

In a 2015 review of cocaine-related deaths from medical examiner and coroner data, the mean and median age of the decedents was 42 (N = 3151). The common sequelae associated with chronic cocaine in patients over the age of 30 include heart disease, myocardial infarction, and exacerbation of chronic disease, strokes, and renal failure. Cocaine use is often associated with violence. This may be due to violent acts caused by the pharmacological effects of cocaine (psychopharmacological model), violent interactions resulting from involvement with an expensive but illicit commodity (systemic model), and violence as an instrumental act to obtain resources to purchase/obtain cocaine (economic-compulsive model). A large percentage of homicide cases are cocaine related. In 1990–1991, 31.3% of homicide cases were positive for cocaine and/or benzoylecgonine in New York City. Detroit reported a 28% positive rate for the parent drug in blood of homicide victims in 2000.

Pharmacokinetics

Absorption

Cocaine is well absorbed from all routes of administration, but the time course and extent of absorption differ among them. The intravenous (IV) route of administration, sometimes called "mainlining," is the only route that consistently produces 100% drug bioavailability. The bioavailability of cocaine by insufflation (IN) or smoked (SM) administration is quite variable; however, the convenience of these two routes of administration and the latter's rapid, intense onset of effects make them the most commonly used.

The time course for the high in humans parallels that of the cocaine concentration in the striatum, a region in the brain implicated in control of motivation and reward. For equivalent plasma cocaine concentrations and DA transporter blockade, SM cocaine induced significantly greater self-reports of "high" than IN cocaine and showed a trend for greater effect than IV cocaine. After either IV or SM administration, the subjective euphoric response occurs in 1–5 min, with a cardiovascular response peaking in 8–12 min and lasting approximately 30 min. After IN administration, a euphoric effect occurs within 15–30 min, cardiovascular changes and plasma concentrations peak within 20–60 min, and effects last several hours but the euphoric effects are attenuated compared to the SM route despite the extended effects.

Metabolism

Cocaine contains two ester moieties, rendering it susceptible to hydrolysis in vitro and in vivo. The alkyl ester of cocaine is hydrolyzed to benzoylecgonine via spontaneous hydrolysis as well as liver methylesterases, and the phenyl ester is hydrolyzed to ecgonine methyl ester by plasma cholinesterase and liver benzoylesterases (Fig. 23.1). Benzoylecgonine and ecgonine methyl ester are both further metabolized to ecgonine which is infrequently analyzed but has

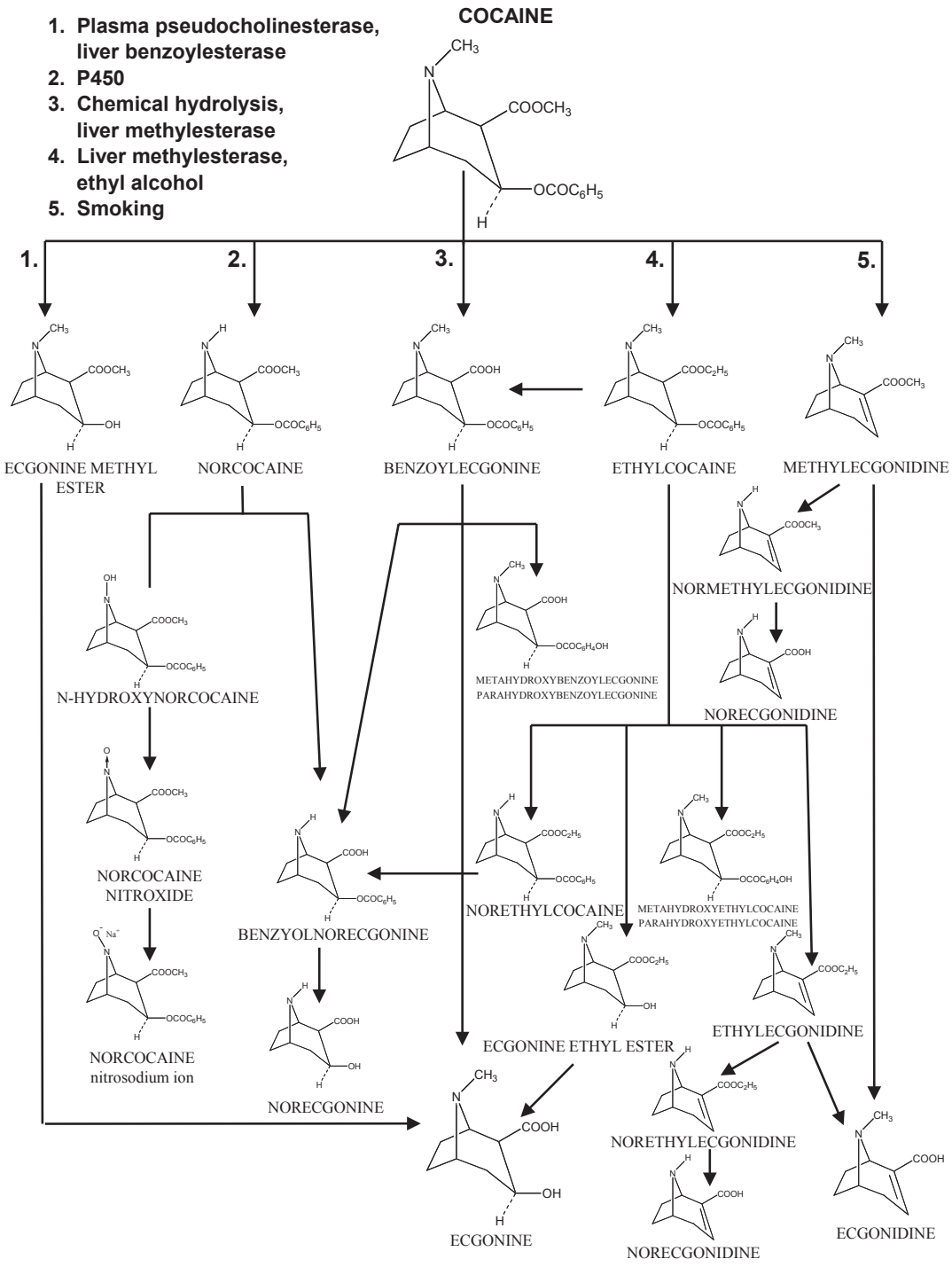

Fig. 23.1 Pathways in the metabolism of cocaine

been reported to be a useful marker of cocaine use, especially in urine. If cocaine is used with ethanol, cocaethylene (or ethylcocaine), produced by the transesterification of cocaine with ethanol, may also be observed. Unlike benzoylecgonine and ecgonine methyl ester which are

inactive metabolites, cocaethylene is an active compound that has been shown to produce even greater euphoria than cocaine itself. The conversion of cocaine to cocaethylene occurs about 3.5 times faster than the conversion of cocaine to benzoylecgonine, thereby potentially increasing the toxicity of cocaine when used with ethanol. Other minor metabolites of cocaine include norcocaine, hydroxylated metabolites, and methylecgonidine, which has been associated primarily with smoked crack cocaine as a thermal decomposition product. Methylecgonidine is further metabolized to ecgonidine which may be a more useful indicator of crack smoking. When smoking cocaine and using ethanol, ethylecgonidine may be produced.

Plasma Concentrations

Many pharmacokinetic studies have been performed with cocaine. Although considerable interindividual variation between subjects has been reported, several observations can be made. When bioequivalent doses of cocaine were administered by the IV and SM routes, similar absorption and elimination curves for cocaine were obtained with dose-related mean peak plasma concentrations. After IN administration, the dose and mean peak plasma concentration showed a poor correlation due to dose-dependent bioavailability by that route. Typical peak plasma cocaine concentrations in most single-dose pharmacokinetic studies by the SM (up to 100 mg), IV (up to 64 mg), and IN (up to 100 mg) averaged between 200 and 400 ng/mL.

For IV and SM routes, the average half-life for cocaine, based on the literature, is about 60 min with a somewhat longer half-life after IN administration (up to 84 min). Benzoylecgonine appears in the plasma within 15–30 min following cocaine administration by the IV, SM, and IN routes of administration. Peak plasma benzoylecgonine concentrations usually occurred within 90 min after SM and IV cocaine administration and were about half the peak cocaine concentrations. After IN administration of cocaine, peak benzoylecgonine concentrations were not reached until 3 h and were about twice that of cocaine and remained elevated for the next 5 h. The rate of benzoylecgonine elimination was slow compared to its rate of formation, accounting for its accumulation in plasma, while cocaine concentrations were decreasing. The elimination half-life for benzoylecgonine was between 5 and 6 h after IV and SM administration and about 3.5 h after IN administration. Ecgonine methyl ester concentrations are usually much lower than those of benzoylecgonine but are present at significant concentrations after oral cocaine administration, suggesting a possible first pass effect of liver benzoylesterase for this metabolite. Ecgonine methyl ester may also form in vitro in blood collected without or with insufficient sodium fluoride preservative as an inhibitor of plasma cholinesterase.

When cocaine is co-administered with ethanol, the appearance of cocaethylene in the blood is delayed by 10–30 min. Mean peak plasma cocaine concentrations were higher when human subjects were given 100 mg of cocaine HCl IN followed by 1 gm/kg of vodka (352 ng/mL) than after 100 mg of cocaine IN alone (258 ng/mL). The mean peak cocaethylene concentration in the subjects receiving both ethanol and cocaine was 55 ng/mL. The average half-life of cocaethylene based on various reports is about 120 min (range 100–148 min). The altered pharmacokinetics in simultaneous cocaine and ethanol use may contribute to increased risk of toxicity.

Excretion

Cocaine and its metabolites are excreted into the urine almost exclusively by simple filtration. Thus, the urinary excretion rates and plasma concentrations of cocaine and benzoylecgonine parallel one another, indicating that the elimination rate of the drug is proportional to the plasma concentration. After a single cocaine dose, 64–69% is recovered in the urine within 3 days, regardless of the route of administration, and 86% of this amount is recovered within the first day. Only a small fraction of an administered dose of cocaine is excreted as parent drug with a majority of the metabolites detected as benzoylecgonine (26–54%) and ecgonine methyl ester (18–41%).

Postmortem data suggest that with chronic use, cocaine concentrations in the urine are much higher than would be expected on the basis of pharmacokinetic data. Urine concentrations of ecgonine, initially thought to be a minor urinary metabolite, have been shown to significantly exceed those of benzoylecgonine in certain situations. In 104 of 139 urine samples in which ecgonine was present at ≥50 ng/mL, the mean ecgonine concentration was approximately five times the comparable benzoylecgonine concentration. On the basis of the benzoylecgonine concentrations, this scenario appears to be most likely during the late stages of urinary excretion of a cocaine dose. No pharmacokinetic studies have yet measured this metabolite, however, and its presence may be due to hydrolysis of benzoylecgonine and/or ecgonine methyl ester.

Direct Methods of Analysis

Immunoassay

Immunoassays are commonly used for screening purposes because they are readily amenable to large-batch analysis, are relatively sensitive, and require little or no sample preparation. Because immunoassays are targeted to detect benzoylecgonine, they are particularly well suited for screening urine samples. Several types of immunoassays are on the market; depending on the product selected, immunoassays use the principle of enzyme immunoassay (EIA), microparticle immunoassay (KIMS), cloned enzyme donor immunoassay (CEDIA), or enzyme-linked immunosorbent assay (ELISA). Although all immunoassay techniques are targeted to benzoylecgonine, cross-reactivities to cocaine and other metabolites vary considerably by manufacturer and analytical principle. Immunoassays that possess substantial cross-reactivity to cocaine are particularly useful for screening oral fluid, hair, and postmortem blood, where significant concentrations of the parent drug might be found. Depending on the immunoassay selected, analysis of postmortem blood and tissue homogenates may be performed directly or after protein precipitation and/or solvent extraction. ELISA is especially well suited to postmortem analyses of whole blood because these assays generally do not require any sample preparation other than dilution. These assays can also be used successfully with tissue homogenates. Although the cutoff concentration for benzoylecgonine in US federal workplace drug testing is 150 ng/mL, most immunoassays can reliably detect far lower concentrations. Immunoassay-based approaches are discussed in more detail in Chap. 13.

Indirect Methods of Analysis

Sample Preparation

Before cocaine and its metabolites can be analyzed with chromatographic techniques, the drugs generally must be separated from the biological matrix. This may be accomplished using a variety of techniques such as liquid–liquid extraction, solid-phase extraction (SPE), and solid-phase microextraction procedures. These are explored in more detail in Chap. 9. SPE and solid-phase microextraction can be readily adapted to laboratory-automation devices. Several important issues must be considered before choosing an extraction procedure, however. Cocaine and many of its metabolites are esters that are susceptible to hydrolysis under alkaline conditions and at high temperatures. In addition, plasma and liver esterases contribute to their hydrolysis. In unpreserved specimens, this should be considered. During sample preparation, the amount of time the biological sample remains in conditions unfavorable for cocaine stability must be minimized; otherwise, esters may hydrolyze in vitro and complicate the interpretation of the analytical results (see "Interpretation of Results"). For this reason, isotopically labelled internal standards are often favored. Consideration must also be given to the targeted analytes because the polarities of cocaine and its metabolites vary considerably.

Other than stability concerns, extraction of cocaine and cocaethylene is straightforward. These compounds are readily extracted into *n*-butyl chloride at pH 8–9. A chloroform–2-

propanol mixture (9:1) is also commonly used. These conditions will also extract benzoylecgonine and ecgonine methyl ester, although not with optimal recoveries. SPE procedures, also used for these analytes, commonly use a protein-precipitation step before applying the buffered supernatant to the extraction column. Elution is typically accomplished with a strongly basic organic solvent (e.g., methylene chloride, 2-propanol, and ammonium hydroxide, 78:20:2). Methodologies for SPE and the different chromatographic supports are discussed in Chap. 9. This approach works well for cocaine and the majority of metabolites of interest (benzoylecgonine, cocaethylene, ecgonine methyl ester). Extraction of the most polar analyte, ecgonine, presents a unique challenge. Because it is both a carboxylic acid and an alcohol, it extracts poorly using conventional approaches.

Thin-Layer Chromatography

Thin-layer chromatography (TLC) is a simple technique that can be used to analyze for both cocaine and benzoylecgonine, but its lack of sensitivity generally limits it to the analysis of urine or bile samples, if it is used at all. Due to a lack of specificity for forensic purposes, it is rarely used today.

Gas Chromatography

Gas chromatography (GC) was the sample introduction technique most frequently used for the analysis of cocaine and its metabolites until use of liquid chromatography (LC) techniques became more frequently employed. Cocaine and cocaethylene can be readily assayed without derivatization by means of nitrogen–phosphorus detection and by mass spectrometry (MS) detection in both the electron ionization and positive chemical ionization modes. Detection by flame ionization may also be used but is not as sensitive. Ecgonine methyl ester and related compounds can be detected without derivatization but tend to tail on most analytical columns because of free hydroxyl moieties. Benzoylecgonine and related compounds must be derivatized prior to analysis. For this reason, in addition to greater sensitivity, LC has largely replaced GC for sample introduction.

When GC is utilized, various derivatization procedures have been used. Acylation procedures (e.g., pentafluoro) and silylation (e.g., trimethylsilyl) derivatize both benzoylecgonine and ecgonine methyl ester. Alkylation procedures (e.g., n-propyl) will derivatize N-desmethyl metabolites in addition to benzoylecgonine. Sequential derivatization allows the simultaneous detection of multiple analytes. For example, ecgonine, ecgonine methyl ester, benzoylecgonine, and norcocaine can be derivatized with 1-propyl iodide followed by *p*-nitrobenzoyl chloride to yield *p*-nitro-*n*-propylcocaine, *p*-nitrococaine, *n*-propylcocaine, and *N*-propylcocaine, respectively. Derivatization techniques are explored in more detail in Chap. 12.

If GC analysis is performed, detection by MS provides the highest degree of specificity of all GC detectors and is virtually a requirement for forensic confirmation of cocaine and its metabolites. A particular advantage with MS detection is that isotopically labelled analogues of cocaine and its metabolites are available for use as internal standards permitting excellent reproducibility and accurate analysis. If other detectors are used, the selection of internal standards should be carefully considered so that they undergo the same chemistry as the analyte.

Liquid Chromatography and Others

Liquid chromatography (LC) has become the most frequent sample introduction technique for the analysis of cocaine and its metabolites due to the need for minimal sample preparation, no need for derivatization, a variety of extremely sensitive and specific detectors, and the ability to use isotopically labeled internal standards. The use of MS and MS/MS detectors along with high resolution MS detectors has created many new approaches for the analysis of xenobiotics including cocaine and metabolites and has resulted in

the virtual elimination older LC-based detectors, such as ultraviolet and diode array detectors.

The newest techniques using MS detectors bypass LC chromatographic sample introduction altogether using ionization sources such as laser diode thermal desorption (LDTD) and matrix-assisted laser desorption/ionization (MALDI) high-resolution mass spectrometry (HRMS). These techniques result in much shorter analysis times, less sample preparation, and the potential for applications to nonstandard matrices. The main disadvantage for the moment is cost.

Interpretation of Results

Pathology

Many pathologic conditions may predispose an individual to cocaine toxicity that may cause death at cocaine concentrations lower than expected. The diagnosis of such conditions will ultimately affect toxicological interpretation. Chronic cocaine use may also contribute to the development of pathologic conditions that may cause sudden death. Excellent texts on the pathology of drug abuse are available, so only the most important conditions will be considered here.

A significant number of deaths have been associated with a cocaine-induced psychosis now commonly known as cocaine-induced excited or agitated delirium. This syndrome is characterized by severe hyperthermia (104° F–108° F), extreme agitation and delirium, respiratory arrest, and sudden death. These individuals exhibit bizarre and violent behavior and extreme strength, and they frequently can be seen running around—sometimes naked—shouting, fighting, breaking things, and causing injury to themselves and others. Death may occur from these injuries, but death more frequently occurs suddenly after agitation has ceased. Unfortunately, the police have usually intervened by this time, and the restrained individual then dies in police custody. At autopsy, minor injuries, especially head injuries that may occur during attempts to restrain an individual, may lead to overinterpretation and litigation. Other autopsy findings are relatively nonspecific, but cardiomegaly is a consistent finding. In these cases, the stress from restraint may produce catecholamine surges on an already sensitized myocardium, producing a terminal arrhythmia. The use of Tasers to try to subdue these individuals further complicates interpretation. In a multiyear review of 75 Taser-related deaths, cardiovascular disease was found in 54.1% of the cases with available autopsy reports. Illegal substances were found in 78.4% of the cases, of which 86.2% involved stimulant drugs and 75.7% had a diagnosis of excited delirium. In 27% of the cases, the use of a Taser was considered a potential or contributory cause of death. This topic remains very controversial, however.

In noncustody excited-delirium cases, decedents are frequently found in places where they may have attempted to cool themselves, such as the bathroom. Other evidence of attempts at cooling (e.g., wet towels and ice cube trays) may also be present at the scene. Toxicology results in excited-delirium cases have demonstrated cocaine-to-benzoylecgonine ratios similar to those found for other accidental deaths due to cocaine toxicity. A large percentage of excited-delirium victims die after they have survived 1–12 h. When the survival time is <6 h, cases featuring high cocaine concentrations also tend to have high benzoylecgonine concentrations, and cases with low cocaine concentrations tend to have low benzoylecgonine concentrations. Because the half-life of benzoylecgonine exceeds that of cocaine, these findings suggest that the development of excited delirium is associated with binge cocaine use.

Although chronic cocaine use may produce toxicity in a variety of organ systems, cardiovascular diseases are most commonly associated with sudden death due to cocaine. Coronary artery disease with or without myocardial infarction, myocardial diseases including myocarditis, hypertrophy, dilated cardiomyopathy, and contraction band necrosis due to catecholamine toxicity, valvular heart disease, and aortic dissection have all been attributed to complications of cocaine abuse. Unfortunately, few features distinguish cocaine-induced disease from naturally occurring pathology. Neurologic disorders have

frequently been associated with chronic cocaine use and may be related to sensitization. Subarachnoid and intracerebral hemorrhages, berry aneurysms, cerebral infarction, and cocaine-induced seizures have all been reported in addition to cocaine-induced excited delirium. At autopsy, chronic cocaine users have a statistically significant decrease in body mass index compared with nonusers, an observation consistent with cocaine's anorectic properties. Interestingly, cocaine users who die after cocaine-induced excited delirium tend to have a high body mass index. Physical signs of cocaine or drug use are also important (e.g., puncture wounds, needle tracks, a perforated nasal septum, evidence of seizures such as lip bites, and drug paraphernalia at the scene or with the individual).

Occasionally, it may be possible to attribute cocaine toxicity or death to "body packing." Body packers may try transporting cocaine by swallowing a cocaine-filled condom (or other container) or concealing it rectally or vaginally. These containers have occasionally ruptured, releasing a large dose of the drug. Blood cocaine concentrations in postmortem cases are usually huge, sometimes >100,000 ng/mL, making interpretation straightforward.

Blood

Many factors must be considered when interpreting cocaine and metabolite concentrations in the blood. Adult (single) doses of cocaine, whether for medical or abuse purposes, are typically in the range of up to 100 mg producing a plasma or blood concentration of 200–400 ng/mL. Toxic doses are highly variable, depending on degree of individual tolerance, route of administration, presence of other drugs, and other factors. In simultaneous ethyl alcohol and cocaine users, cocaethylene concentrations should also be considered when interpreting results. Plasma cocaine concentrations >1000 ng/mL have been reported without adverse effects in some studies after chronic oral dosing and after repeated doses of smoked cocaine. Concentrations of >5000 ng/mL have generally only been reported in fatal cases, although concentrations in fatalities are usually much lower.

A search of the literature suggests that cocaine concentrations of <300 ng/mL are generally considered clinically therapeutic; however, clinical and postmortem studies have clearly shown that therapeutic, toxic, and lethal cocaine concentrations overlap. Tolerance and sensitization may play a significant role in the poor correlation observed. In a study of 130 patients who presented to an emergency room with acute cocaine toxicity, the mean plasma cocaine concentration was 340 ng/mL (range, 0.00–3920 ng/mL). The median cocaine concentration in these patients was only 70 ng/mL; however, the mean and median benzoylecgonine concentrations in these patients were 1570 ng/mL and 1060 ng/mL, respectively. There was no correlation of the cocaine and metabolite concentrations in these patients with their clinical state or outcome, but the degree of symptoms of toxicity—most notably hyperthermia, heart rate, and psychosis—was a better predictor of patient outcome.

Given that cocaine is typically used in a binge of multiple doses over the course of many hours, blood concentrations of cocaine and its metabolites are usually not useful for estimating the dose or time of administration. Because the half-life of benzoylecgonine is considerably longer than that of cocaine, one would expect benzoylecgonine concentrations to increase out of proportion to the cocaine concentration during a cocaine binge. High blood benzoylecgonine concentrations with significant cocaine concentrations (>100 ng/mL) may indicate binge cocaine use, whereas similar cocaine and benzoylecgonine concentrations are more typical of a recent single dose or multiple doses within a very short period of time.

As previously discussed, cocaine stability after collection and during analysis may create analytical artifacts that may alter interpretation of the results. Blood samples collected in the hospital, in particular, are usually collected in containers without preservative and may not have been stored in refrigerated conditions. In unpreserved blood, in vitro stability studies have shown that cocaine is hydrolyzed almost exclusively at the

phenyl ester by plasma pseudocholinesterase to yield ecgonine methyl ester. The rates of hydrolysis of both esters have been shown to be temperature and pH dependent, with higher temperatures and pH increasing the rate of hydrolysis. The loss of cocaine in unpreserved blood can be dramatic with 50% losses in a matter of hours at room temperature. Ideally blood samples should be preserved with 1–2% sodium fluoride w/v. Many fluoridated gray-top tubes do not contain sufficient sodium fluoridate for adequate long-term preservation. Additionally, while sodium fluoride minimizes pseudocholinesterase-mediated hydrolysis to ecgonine methyl ester, it does not prevent pH and temperature-dependent conversion of cocaine to benzoylecgonine, so refrigeration or freezing of preserved samples is still recommended.

For postmortem cases, heart blood should be collected only during the autopsy to ensure that the hypodermic syringe is aspirating blood directly from the heart. If no autopsy is performed, only peripheral blood should be collected because samples collected by "blind stick" are prone to contamination. In addition, trauma may yield contaminated blood samples. Ideally, both peripheral blood and heart blood should be collected.

Ultimately, history and investigation, laboratory findings, witness reports and field sobriety tests or drug recognition expert evaluations for human performance cases, clinical presentations, or autopsy results must all be considered together because any factor taken out of context may produce an incorrect interpretation.

Urine

Most clinical tests for cocaine, whether for hospital drug testing or workplace drug testing, are performed on urine using immunoassays. These drug screens are designed to detect benzoylecgonine. Benzoylecgonine cutoffs on urine toxicology screens under the US federal drug testing program are 150 ng/mL with a 100 ng/mL confirmation cutoff. Hospital toxicology screens may use different cutoff concentrations.

Urine is suitable only for determining an exposure to cocaine. Quantitative measurements of benzoylecgonine (especially if corrected for creatinine) in serial urine samples may be useful in substance-abuse treatment programs to detect a relapse during a period of abstinence, but single samples cannot be similarly interpreted because only a randomly collected urine sample is typically analyzed. Benzoylecgonine is typically detected for as long as 1–3 days after a single use; however, chronic cocaine use can increase this significantly. Prolonged positive immunoassay results for 5–10 days have been reported after compulsive cocaine use, with continuous positive results for up to 16 days with a longer terminal half-life after chronic, heavy cocaine use. With chronic and/or binge cocaine use, urine benzoylecgonine concentrations can exceed 100,000 ng/mL, while low-dose, single-use concentrations are much lower.

Issues concerning the stability of benzoylecgonine have been raised, particularly with regard to retesting a sample previously reported as positive. Benzoylecgonine, although relatively stable in urine when frozen, is susceptible to hydrolysis in alkaline conditions and at higher temperatures. An additional concern is that cocaine in urine can hydrolyze to benzoylecgonine in alkaline conditions and higher temperatures.

In human performance and pediatric exposure testing, issues are frequently raised regarding unknowing exposure or ingestion of cocaine. Passive exposure to cocaine smoke under extreme conditions can produce detectable benzoylecgonine in urine but at concentrations below the threshold used in workplace drug testing. If testing at lower concentrations, data should be interpreted carefully. Another issue often raised is that cocaine ingestion was unknowing because the cocaine had been added to a beverage. Studies have been performed with ingestion of coca-containing teas from South America and cocaine-fortified beverages. These studies demonstrate that very small amounts of cocaine (<5.0 mg or about one-fifth of a typical IN dose or line) added to or contained in a beverage are sufficient to produce a positive result in a drug test for cocaine metabolites in urine in an unsuspecting individual. In such cases, the detection of unique cocaine

metabolites, such as methylecgonidine or ecgonidine, which are produced after smoking crack cocaine, may prove to be useful for refuting alleged oral ingestion of cocaine after a positive drug-test result for benzoylecgonine.

Concern has also been raised regarding passive exposure to cocaine in personnel who come in frequent contact with the drug. The issue of dermal exposure to cocaine has been investigated in several studies, all of which demonstrated that with appropriate personal protective equipment, casual exposure to cocaine is not likely to produce a benzoylecgonine concentration greater than the 150 ng/mL US federal workplace drug-testing cutoff concentration.

Tissues

Brain may be a useful specimen for the measurement of cocaine and its metabolites because cocaine is relatively stable in the brain and is not subject to postmortem redistribution. Because cocaine rapidly crosses the blood–brain barrier, brain cocaine concentrations in cases of acute cocaine intoxication have been shown to be much higher than concentrations in the blood. In addition, because benzoylecgonine probably does not cross the blood–brain barrier, the presence of this metabolite in the brain has been attributed to cocaine that entered the brain. Thus, the brain may be particularly helpful in estimating the pattern of cocaine use before death. In a study of 34 acute cocaine deaths, the mean brain-to-blood ratio of cocaine concentration was 9.6 (median ratio, 3.8), compared with a mean ratio of 2.5 in 14 incidental cases in which both analytes could be detected. Cocaine was also detected in the brain in 11 incidental cases in which only benzoylecgonine was detected in the blood. The mean cocaine-to-benzoylecgonine ratio was also higher in the brain than in the blood, both in acute cases (14.7 vs 0.64) and in incidental cases (0.87 vs 0.27). These observations have been replicated in other studies. The main disadvantage of the brain is the difficulty of working with fatty homogenates, although SPE technology has simplified sample handling to some degree.

Other tissues may be useful when biological fluids are not available, but they do not provide additional interpretive information. In the few cases studied, kidney and spleen have been found to have the highest cocaine concentrations.

Hair

Cocaine and metabolites may be detectable in hair for longer periods of time than urine. For this reason, analysis of hair may be useful in determining a past history of cocaine use. It takes 4–5 days for ingested cocaine to begin to appear in the hair. The ability to detect cocaine in hair is based more on the concentration than on a pharmacologic "time window," because as long as the hair is not cut, the incorporated drug will remain in it. However, the utility of hair is limited to obtaining historical information about drug use and is not useful for determining an acute use, such as in post-accident testing. As such, hair testing may be extremely useful in postmortem cases in which no other specimen is available. Hair has even been used to identify cocaine use in ancient Peruvian mummies.

Although appropriate forensic methodologies exist for the analysis of cocaine and metabolites in hair, their use for employment-related drug testing is controversial because of a lack of the data required for accurately interpreting the results. Still under study are many important issues related to hair testing, including environmental contamination, washing techniques, racial bias in hair due to the concentration of certain types of melanin, sex bias, sample adulteration, quality-control procedures, proficiency testing, and the establishment of cutoff concentrations.

The primary analyte detected in hair after cocaine use is the parent cocaine, but to minimize environmental-contamination issues and to demonstrate cocaine ingestion, the proposed guidelines for hair testing in federal workplace drug-testing programs require a benzoylecgonine/cocaine ratio of ≥ 0.1 in the confirmatory testing process in order to report a positive result. Still, some studies suggest that benzoylecgonine arises primarily from hydrolysis of cocaine in hair, not

from biological incorporation. Other possible target analytes in hair for demonstrating in vivo cocaine use include norcocaine and cocaethylene.

Oral Fluid

Oral fluid may be a useful specimen for detecting recent cocaine use in human performance and workplace drug testing. There is generally a good correlation between saliva and plasma cocaine concentrations. Saliva cocaine concentrations have also been correlated to behavioral effects. In addition, saliva may be collected by direct observation without any invasive procedure.

Appropriate sample-collection procedures are critical for minimizing contamination from the oral cavity, especially after SM and IN administration. The use of benzoylecgonine as a target analyte in workplace testing should help minimize this issue. Despite cocaine being the predominant analyte in saliva after acute cocaine use, benzoylecgonine is detected more frequently and at higher concentrations than cocaine after cessation of chronic cocaine use. Detection times for benzoylecgonine after chronic oral cocaine administration were comparable for saliva and plasma (45 h vs 47 h, respectively; cutoff, 10 ng/mL) but were far less than for urine, which had a mean *minimum* detection time of 165 h for the same low cutoff concentration. On the other hand, cocaine could be detected for nearly twice as long in saliva than in plasma (15 h vs 9 h; cutoff, 10 ng/mL). The saliva/plasma cocaine ratio can also be affected by saliva pH and saliva flow rate after stimulation. For this reason, it is important to develop standardized collection protocols.

Sweat

Sweat may be a useful, noninvasive specimen for monitoring drug use. Sweat may be collected by means of a collection patch placed on the skin for a predetermined period. This collection procedure allows a continuous period of monitoring or accumulation of any excreted drug. In sweat, cocaine is excreted primarily as the parent drug, offering the added advantage of simple GC analysis. Depending on the device used to collect sweat, any attempt at tampering with the collection device would be evident. Although wearing a sweat patch for monitoring cocaine use may provide a wider detection window than for urine, any correlation between the accumulated sweat cocaine concentration with the degree of impairment or time of use is not likely. Because trace amounts of cocaine can be detected in sweat after IV administration of as little as 1 mg cocaine, some concerns regarding passive exposure have been raised.

Effect of Cocaine on Driving

Apart from the effects of cocaine, driving performance entails many factors that may affect driving, including coordination skills, reaction time, risk-taking, emotional state (e.g., anger, fear, stress, hostility), personality style (relaxed, tense, aggressive), fatigue, physical and mental health, and distractions (radio, cell phone, smoking, thoughts, conversation, children). Whether a crash could have been prevented in the absence of a drug(s) given the inherent driving performance variables is difficult to determine.

Relatively few scientific studies have evaluated the effects of cocaine on driving performance. The euphoric effects of cocaine during acute intoxication may give a driver the feeling of increased mental and physical abilities, and this optimism has been suggested to prompt increased risk-taking behavior and perhaps increase the probability of crashes, particularly in conjunction with ethyl alcohol use. In one study, 62% of cocaine smokers reported symptoms of suspiciousness, distrust, and paranoia. These effects have led to high-speed chases with police. It is not surprising that the use of stimulants has also been associated with road rage.

These findings appear consistent with an examination of 253 motor vehicle fatalities that occurred in metropolitan Detroit (Wayne County, Michigan) over a 3-year period. Cocaine and/or its metabolites were detected in the blood of 25 (10%) of these cases. An analysis of the histories confirmed that aggressive driving (as determined

by high speed and loss of control) was the most common finding in all of the crashes and occurred in all but three cases. Ethyl alcohol was detected in 14 of the 25 cases, ten of which were also positive for parent cocaine and/or cocaethylene in the blood, confirming the high incidence of acute combined cocaine and ethanol use. However, although high-risk driving appeared to be associated with cocaine use (with or without ethyl alcohol), fault is more likely to occur when ethyl alcohol is present, indicating that alcohol may play a larger role in crash occurrence than cocaine. This fact is consistent with other studies that compared crash responsibility with drug and alcohol use and may be related to the combined effects of a stimulant drug with a drug that depressed inhibitions. There was no evidence to suggest that the concentration of cocaine and its metabolites was related to crash occurrence.

In a study of more than 25,000 drivers in Sweden arrested for driving under the influence of drugs, 795 were positive for cocaine and/or benzoylecgonine in the blood (in the absence of alcohol). In the 20 cases with the highest cocaine concentrations in the blood, drivers were observed to be driving dangerously, including weaving, speeding, and ignoring red lights. Typical findings reported by police officers included increased pupil diameters, bloodshot eyes, agitation, difficulty standing or sitting, incoherent speech, and increased pulse rate. However, a review of 44 reports by drug-recognition experts in cocaine-related driving-under-the-influence cases in Washington state showed that although increased pupil diameter (especially in a dark room) and pulse rate were frequently observed, the magnitude of these changes did not appear to be related to cocaine concentration.

The ability of cocaine to produce mydriasis appears to have significant effects in self-reported observations. After IN cocaine use, 43% of individuals reported increased sensitivity to light, halos around bright objects, and difficulty focusing. More than 34% of cocaine smokers reported blurred vision, often accompanied by glare-recovery problems. Hallucinations were reported by 50% of cocaine smokers and 18% of IN users. "Snow lights," flashes or movements of light in the peripheral field of vision, were the most commonly reported hallucination. Reaction to snow lights included moving in their direction or trying to avoid or evade them.

When self-reported driving behaviors were compared for individuals in treatment for cocaine or cannabis abuse, individuals reported reckless driving 29.7% of the time when driving under the influence of cocaine, compared with only 2.4% of the time when driving under the influence of cannabis. Conversely, individuals driving under the influence of cannabis reported that they were more likely to attempt to drive carefully or cautiously (27.9%) than when driving under the influence of cocaine (11.8%).

Because the effects of cocaine are brief, the crash that follows cocaine use may be a particularly dangerous time for driving; however, samples collected from individuals in such a state may be positive only for cocaine metabolites, making assessment difficult. The presence of cocaine metabolites suggests past use and cannot be used to determine impairment or withdrawal without additional information, such as witnessed driving and/or observations by a trained drug-recognition expert. This is particularly the case when only a urine sample is available. Of 150 individuals arrested for reckless driving and who tested negative for alcohol, 13% tested positive for cocaine metabolites, 33% were positive for cannabinoids, and 12% were positive for cannabinoids and cocaine metabolites in the urine. Nearly half of the drivers testing positive for prior cocaine use performed normally on field-sobriety tests, including two individuals who were stopped for driving directly into oncoming traffic. Of those testing positive for cocaine, 21% were sleepy or slow; 39% were happy, carefree, and talkative; and 39% were combative, argumentative, and paranoid.

Double-blind laboratory studies have demonstrated that low doses of cocaine may actually improve driving performance and counteract some of the performance decrements of ethyl alcohol and other depressant drugs. In a study of more than 4000 individuals, an increased risk of injury was associated with the use of psychoac-

tive substances, but the risk was lower when cocaine was used with other depressant drugs. Although stimulants (amphetamines or cocaine) may acutely enhance performance of simple tasks, this enhancement may disappear as the complexity of the task increases. For example, cocaine-induced hyperexcitability has led to rapid steering or braking reactions in response to sudden sounds, such as horns or sirens.

The current data suggest that it is very difficult to predict driving impairment on the basis of the presence of cocaine and or its metabolites in biological samples alone. Witnessed driving behavior and examination by a drug-recognition examiner, coupled with laboratory studies, is the triad that appears most appropriate for determining driving impairment.

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