Cocaine: Acute Toxicity and Presumptive Testing

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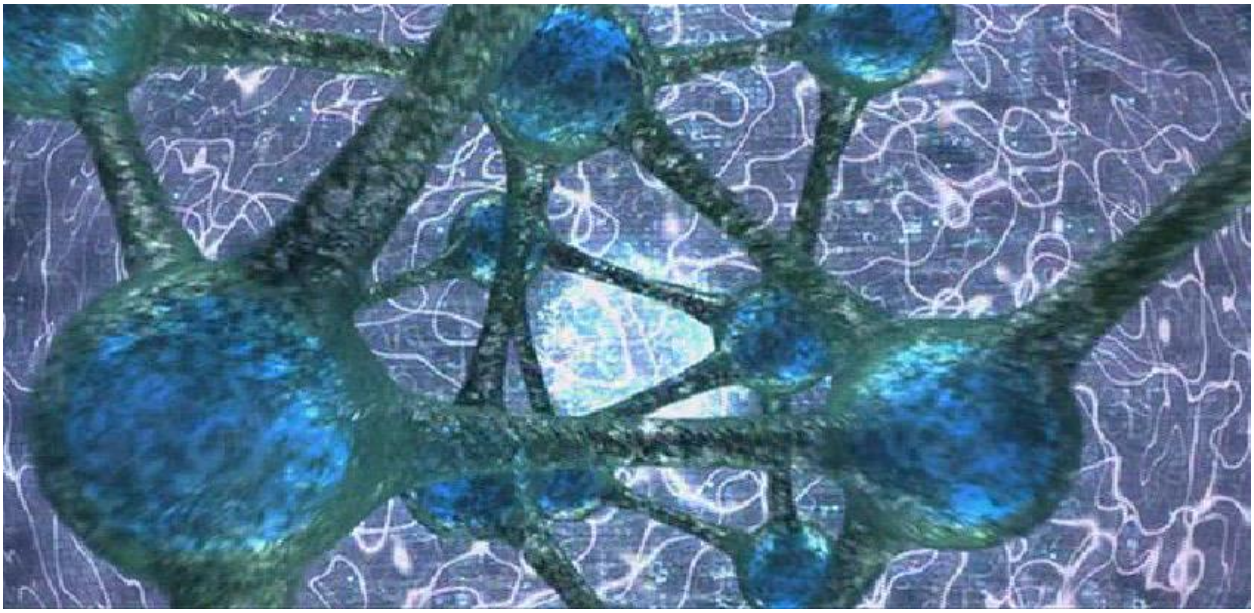

Cocaine remains a popular drug of abuse, and per HHS (2008) of 6.5 million US Federal workplace drug tests, about 40,000 were positive for cocaine in 2007. Drug testing for cocaine is based on the metabolite benzoylecogonine which is detectable in the user's urine for 24 hours, possibly even up to 72 hours. Non-metabolized cocaine may only be detectable for 4-6 hours following use, making it a less useful target in a drug testing program.

Cocaine has sodium channel blocker actions, which provide anesthetic properties, but also potential cardiotoxic effects. It also blocks the reuptake of neurotransmitters norepinephrine, dopamine, and serotonin. Blocking the reuptake of norepinephrine results in adrenergic effects observed as mydriasis, vasoconstriction, hypertension, tachycardia, and tachypnea. These are important effects clinically, and can be observed on physical examination. The desirable effects of cocaine are mediated by the neurotransmitter dopamine. The positive effects of acute cocaine intoxication include intense euphoria, mental energy, heightened sexual excitement, increased self-confidence, and elevation of mood. Potential undesirable effects of excess dopamine include paranoia, hallucinations, and dysphoria. Following an acute dose of cocaine, brain concentrations of dopamine increase briefly and then decrease markedly to below normal concentrations. This corresponds to a central stimulatory "rush" and "crash" experienced by the cocaine user.

Cocaine increases dopamine by preventing the reuptake of dopamine into the presynaptic dopaminergic neuron by binding to receptors on the dopamine transporter. Dopamine reuptake is mediated by sodium, chloride, and energy dependent active transport, and becomes inhibited when cocaine binds to the sodium binding site. This action also alters the

chloride binding site, thus preventing the binding of both sodium and chloride ions. Because translocation of dopamine across the membrane of the presynaptic neuron is inhibited, increased extracellular dopamine concentrations are available to chronically stimulate the dopamine receptor in the postsynaptic neuron.

Cocaine excited delirium is a potential complication of cocaine use which is associated with hyperthermia, delirium, agitation, cardiorespiratory arrest, and sudden death. It is thought to occur if the dopamine transporter fails to upregulate as it does in most chronic users. The most common clinical complications following acute cocaine intoxication include profound central nervous system stimulation, with psychosis and repeated grand mal convulsions, ventricular arrhythmias, respiratory dysfunction and ultimately respiratory failure. Other symptoms include mydriasis, hypertension preceding hypotension, and small muscle twitching which may produce extreme hyperthermia. A coma or acute myocardial infarction can occur even after a single use of cocaine. 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 may result in a cerebral aneurysm or hemorrhage.

Cocaine may be administered via intranasal, intravascular, oral, or smoking routes. Cocaine is usually not administered orally because first pass effects (being metabolized by the liver prior to going to the brain) produce low bioavailability (about 20%). Cocaine is metabolized primarily to benzoylecgonine. The mechanisms of cocaine metabolism are not straightforward, however, it is understood that benzoylecgonine is only present in biological samples from the metabolism of cocaine, which is why it is the targeted metabolite for US Federal workplace drug testing programs.

With intranasal, intravascular or smoking routes, cocaine plasma levels rise quickly. There is a rush, followed by a positive drug effect which may last an hour or more. It is also during this time, however, that potentially fatal complications are most likely, as well as the potentially negative side effects may be experienced. Ellefsen, et al. (2016) measured plasma cocaine levels and oral fluid cocaine levels following intravenous administration of 25 mg cocaine. The rush effect was experienced with rising plasma cocaine levels, which peaked at plasma concentration of 1000 mcg/L in the first minute. Oral fluid cocaine levels peaked at about 30 minutes, well after the rush was over. The reported good drug effects lasted for approximately one hour. Physiologic effects of increased systolic blood pressure and increased heart rate were statistically significant 5 and 10 min, and at 15 min for systolic blood pressure only. Plasma cocaine levels were approximately 200 mcg/L after 15 minutes.

Cocaine is a potent sympathomimetic drug, and the most serious consequences of using cocaine are the cardiac and cerebrovascular complications. Sodium channel blockade results in increased myocardial contractility, heart rate, systemic arterial pressure, and myocardial oxygen demand. Cocaine related fatalities have been linked to cardiac events such as

ventricular arrhythmias, tachycardia, systemic hypertension, acute myocardial infarction, and left ventricular hypertrophy. Some of these effects result from chronic use, but a single use of cocaine in a susceptible individual at an adequate dose can be fatal. Pilgrim, Woodford, and Drummer (2013) reviewed 49 post-mortem cases of cocaine in sudden and unexpected death. Thirteen of these cases (determined to have died from drug toxicity and not external injury or natural disease) had non-metabolized cocaine at concentrations ranging 0.01-3 mg/L, with an average concentration of 0.46 mg/L. In comparison to the study above, 0.46 mg/L is equivalent to 460 mcg/L. Twenty cases had benzoylecgonine at concentrations ranging from 0.1-33 mg/L, averaging at 3.26 mg/L.

Immunoassays for cocaine are presumptive tests targeted to detect benzoylecgonine. They are commonly used for screening purposes because they are readily amenable to large batch analysis, are sensitive, and require little to no sample preparation. Immunoassays that are utilized for presumptive testing may include an enzyme immunoassay, micro-particle immunoassay, cloned enzyme donor immunoassay, or enzyme linked immunosorbent assay. All are targeted at benzolyecgonine and their cross-reactivities to cocaine and other metabolites vary considerably by manufacturer and their specific analysis. Immunoassays that possess substantial cross-reactivity to cocaine and ethylcocaine (from ingestion of alcohol with cocaine use) are particularly useful for screening oral fluid, hair, and postmortem blood, where significant concentrations of the parent drug might be found. The presence of benzoylecgognine above the cutoff of 150 ng/mL does not give much information about when the drug was last used. An acute intoxication within hours of death could lead to a below cutoff level with elevated cocaine, making the cross-reactivity useful. Per Vidal et al. (2016) a benzoylecgognine/cocaine ratio of less than 100 is indicative of use within the past 10 hours. The lower the ratio, the more recent the use. Non-metabolized cocaine in the blood suggests recent cocaine use, most likely within 6 hours. Although immunoassays are specifically for detecting benzoylecgognine, they often cross-react to cocaine, and may be positive if cocaine is present even if boenzoylecgognine was below the limit of detection. If the presumptive testing was more specific to benzoylecgognine, it may miss the opportunity to detect a more recent use of cocaine in a post-mortem investigation.

References:

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6. Image from https://www.flickr.com/photos/35872763@N07/