CHAPTER 154

COCAINE AND OTHER SYMPATHOMIMETICS

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PERSPECTIVE

Cocaine, a naturally occurring plant-derived alkaloid, has been used for centuries as a medicinal product. For thousands of years in South America, the leaves of the coca plant (*Erythroxylon coca*) have been chewed for treatment of various ailments. In 1860, the pure alkaloid form was isolated and became a popular constituent of various beverages, pharmaceuticals, and therapeutic tonics, but it was banned from these products in the United States in 1914. At the peak of the cocaine epidemic in the early 1990s, it was estimated that 5 million people used cocaine regularly in the United States.[1] The drug is still popular, with up to 1.6 million current users of cocaine reported as of 2009.[2] This is a decrease from 2.3 million users in 2003,[3] but the consequences of recreational cocaine use are still profound. Cocaine is implicated in violent deaths and was detected in 25% of autopsies of fatal injuries in adults aged 15 to 44 years.[4] In 2009, 39% of drug misuse deaths were due to cocaine.[5] According to the Drug Abuse Warning Network, there were more than 423,000 cocaine-related emergency department (ED) visits representing 52% of drug abuse or misuse cases.[6] As of 2009, cocaine ranked within the top three causes of illicit drug–related deaths at various cities across the United States.[7]

Amphetamines are stimulants originally designed for use as decongestants and dietary aids that became popular as recreational drugs in the mid-20th century. By modification of the amphetamine molecule, illicit "designer" amphetamines are inexpensively produced. The enhanced effects from these alterations add to the popularity of drugs such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamines. Cocaine, amphetamines, and derivatives of amphetamines are called *sympathomimetics* (Box 154-1). These agents cause central nervous system (CNS) stimulation and a cascade of adrenergic physiologic effects. As of 2009, there were 502,000 methamphetamine current users in the United States.[2]

PRINCIPLES OF DISEASE

Pathophysiology of Cocaine

Acute cocaine use causes release of dopamine, epinephrine, norepinephrine, and serotonin. These neurotransmitters act on different receptor subtypes to cause many effects, but the most important is adrenergic stimulation by norepinephrine and epinephrine (see Box 154-1). Norepinephrine causes vasoconstriction by stimulation of alpha-adrenergic receptors on vascular smooth muscle. Epinephrine increases myocardial contractility and heart rate through stimulation of beta$_1$-adrenergic receptors. In addition to catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited, altering the normal balance between excitatory and inhibitory tone in the CNS. Subsequent stimulation propagates peripheral catecholamine release (Fig. 154-1). Reuptake of serotonin is similarly inhibited and can cause serotonergic excess as well.

Cocaine also is a local anesthetic agent, slowing nerve impulses from neuronal pain fibers by blocking the inward movement of sodium across cell membranes (phase 0 of the action potential).[8] Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmics, is responsible for the occasional conduction abnormality with acute cocaine toxicity.

Cocaine metabolism occurs in the liver and the plasma. In the liver, the drug is metabolized primarily to the active metabolite norcocaine, which potentiates the parent drug. In the plasma, cocaine is metabolized to ecgonine methyl ester through pseudocholinesterase (plasma cholinesterase). This difference may account for the differences in duration of action with different routes of administration.[9] Ecgonine methyl ester may be protective because it is a vasodilator. Genetic differences in the phenotypic expression of plasma cholinesterases may account for individual differences in susceptibility to cocaine toxicity.[10]

Benzoyl ecgonine, a metabolite found in the plasma, is produced primarily from nonenzymatic reactions. It is the metabolite identified by urine toxicology screens. Methylecgonidine and its metabolite ecgonidine are products of cocaine pyrolysis (crack). Although it is less commonly assayed, methylecgonidine also can be identified in the urine. The use of ethanol with cocaine forms cocaethylene, a metabolite that may potentiate the drug's stimulatory effects and lengthen the duration of its effects.[11]

Cocaine Formulations

Unpurified cocaine paste is converted to usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as crack cocaine. It is inhaled with use of a special "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action (Table 154-1). The water-soluble salts of cocaine (cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is insufflated intranasally or dissolved and injected intravenously. Oral administration is rare except for patients who are smuggling or concealing drugs.

CLINICAL FEATURES

The primary clinical effect of cocaine is the excitation of the sympathetic nervous system. Patients with moderate toxicity are alert and awake but may have diaphoresis, tachycardia, mydriasis, and

hypertension without organ damage. A more severely toxic patient may be agitated, combative, and hyperthermic. End-organ damage is rare but may be manifested as an acute hypertensive emergency. Patients may present with focal acute pain syndromes, circulatory abnormalities, delirium, or seizures.

The clinical presentation depends on the dose, route of administration, and time to presentation after drug use. Additives, contaminants, or other drugs may alter the classic signs of acute cocaine toxicity. Patients who are "speedballing," using intravenous heroin and cocaine together, may be initially sedated, and administration of naloxone may precipitously reveal the underlying cocaine intoxication.

Death due to acute cocaine overdose is significantly higher on days with ambient temperatures higher than 88°F.[12,13] The profound diaphoresis associated with cocaine may be absent or limited in cooler environments or if the patient is excessively salt and water depleted.

Initial assessment and treatment should focus on rapidly fatal complications, specifically hyperthermia, hypertensive emergencies, and cardiac dysrhythmias.

Box 154-1 Clinical Effects of Sympathomimetics

Hypertension	Diaphoresis
Hyperthermia	Central nervous system excitation
Tachycardia	
Mydriasis	

Hyperthermia

Acute psychomotor agitation with delirium increases the risk of hyperthermia.[14] Cocaine toxic patients have increased motor tone and generate heat. Vasoconstriction and salt and water depletion can compromise cooling, resulting in life-threatening hyperthermia with core temperatures exceeding 106°F (41.1°C). Delay in recognition and management increases the likelihood of death. Even with a normal temperature, increased motor tone can release intramuscular creatine kinase, with rhabdomyolysis and its attendant renal and electrolyte complications.[15]

Hypertensive Emergencies

Acute cocaine-induced hypertension can seriously injure the cardiovascular system and CNS. Reported sequelae include aortic

Table 154-1 Cocaine Pharmacology by Route of Administration

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	"Crack"	8 s	2-5 min	10-20 min
Intranasal	Cocaine HCl	2-5 min	5-10 min	30 min
Intravenous	Cocaine HCl	Seconds	10-20 min	60-90 min
Oral	Cocaine HCl	30-60 min	60-90 min	Unknown
"Skin popping"	Cocaine HCl	Unknown	Unknown	Unknown

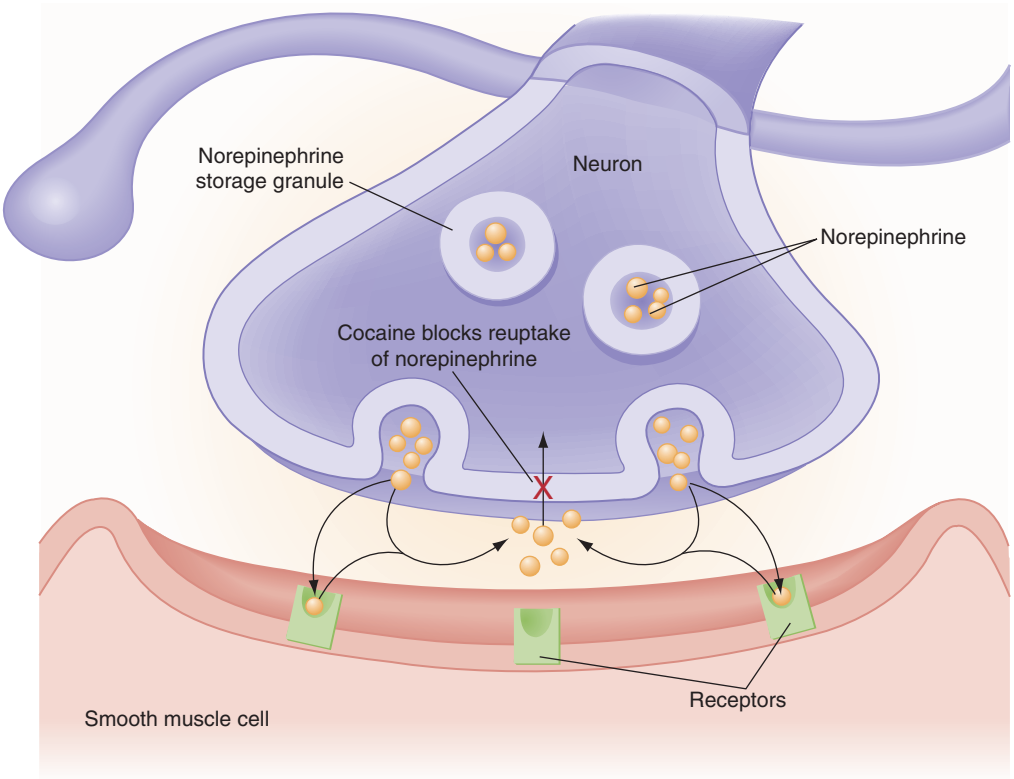

Figure 154-1. How cocaine increases sympathetic tone by increasing neurotransmitters in the synapse.

dissection,[16] pulmonary edema,[17] myocardial ischemia and infarction,[18] intracranial hemorrhage,[19] strokes,[20] and infarction of the anterior spinal artery.[21] Vasospasm can also compromise perfusion to various organs. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers with large oral ingestions.[22,23] Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.[24]

Cardiac Dysrhythmias

Although sinus tachycardia is most common, atrial fibrillation and other supraventricular tachycardias can occur as a result of the surge in catecholamines. A life-threatening dysrhythmia may not be noted until cardiac output abruptly diminishes and the patient suddenly loses consciousness. Torsades de pointes[25] or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms.[8] Transient conduction abnormalities consistent with a Brugada-type pattern are associated with cocaine.[26,27] Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Other Complications

People who binge with continuous use for an extended time have a prolonged state of arousal, which causes catecholamine depletion, salt and water depletion, and poor nutrition. After the acute effects of cocaine have subsided, these patients with "cocaine washout" are profoundly sleepy but arousable and oriented, with normal vital signs or a mild sinus bradycardia.

A patient occasionally has "crack dancing," a transient choreoathetoid movement disorder probably related to abnormalities in dopaminergic tone.[28] Deep venous thrombosis is reported with cocaine use, probably secondary to effects on coagulation. Paranoia, either drug induced or from underlying psychiatric illness, may occur even after the acute effects of the drug subside. The neuropsychiatric effects of cocaine can alter behavior and judgment, increasing the risk of violent injuries.

Complications also arise from the route of administration of cocaine. Inhalation of crack cocaine may cause oropharyngeal burns from the high temperature required to volatilize the drug.[29] Pneumothorax, pneumopericardium, and pneumomediastinum occur from inhalational barotrauma.[30] Intranasal cocaine use is associated with sinusitis and nasopalatine necrosis or perforation.[31] Intravenous users have a high risk of infection with bloodborne viruses, local abscesses, and systemic bacterial infections, including botulism and endocarditis.[32] Transdermal injection of cocaine, or "skin popping," has similar types of complications, especially of skin abscesses. For a chronic user, addiction, or psychological dependence, is mediated through specific dopaminergic neurotransmitter pathways. Although there are no well-defined syndromes constituting cocaine withdrawal, patients have strong cravings for the drug or a general feeling of dysphoria that is not physiologically life-threatening.[33]

In 2009, as much as 69% of cocaine imported into the United States contained levamisole, a veterinary anthelmintic agent.[34] Agranulocytosis, vasculitis with thrombosis, dermal ulcers, and purpura, often affecting the earlobes, occurred as a result of the unintentional exposure to levamisole.[34-37] The reason for this adulteration of cocaine with levamisole is not clear.

DIAGNOSTIC STRATEGIES

Urine drug screening is unlikely to change treatment because it measures a cocaine metabolite (benzoyl ecgonine) that persists for at least 3 days after last use. In a few circumstances, however, urine drug screening may be beneficial to document possible abuse or neglect in a child with suggested exposure, to confirm cocaine as the unknown substance in body packers, and to differentiate paranoia from drug-induced or psychiatric causes.

An electrocardiogram (ECG) screens for dysrhythmias and conduction abnormalities from ischemia, hyperkalemia, or, more precipitously, QRS prolongation from sodium channel blockade. This blockade slows myocardial depolarization and results in a wide-complex tachycardia. The axis may be indeterminate or have a terminal rightward axis deviation similar to cyclic antidepressant toxicity. Cyclic antidepressants and cocaine share class IA antidysrhythmic effects. Evaluation of chest pain is challenging because ST segment elevation is confounded by the presence of early repolarization.[38,39] Serial ECGs may be helpful.

Creatine kinase (CK), a nonspecific marker for muscle injury, is often elevated with cocaine use. The serum CK-MB fraction, troponin I, and troponin T are more specific in patients with atherogenic coronary disease but less certain in patients with cocaine-related chest pain.[33,39,40] Some patients with elevations in CK-MB have normal troponin I or troponin T levels.[40] Patients presenting with positive troponin I and chest pain after cocaine use have a higher incidence of angiographic findings,[41] but up to 18% of patients may have normal angiograms in the setting of positive biomarkers for myocardial infarction (MI).[42] Although the sensitivity and specificity of troponin and other serum enzyme markers are still being investigated for cocaine-related chest pain, cardiac enzymes should be measured as is done for other cardiac patients. Data regarding the role of coronary computed tomography angiography (CTA) to identify patients with cocaine-related coronary disease are evolving.[43,44] Until it is further studied, coronary CTA cannot be routinely recommended.

Severe, persistent headache despite normalization of blood pressure may occur with a subarachnoid hemorrhage and warrants head computed tomography and, if the scan is normal, lumbar puncture. Urine should be checked for myoglobin to screen for rhabdomyolysis.

In the rare event that a patient presents with agranulocytosis or vasculitis suggestive of levamisole, a special laboratory evaluation for urine levamisole by gas chromatography–mass spectrometry may be requested. The sample is ideally obtained within 48 hours after last use.[37] Other infectious or rheumatologic causes of this presentation should also be considered.

DIFFERENTIAL CONSIDERATIONS

A differential diagnosis of acute cocaine toxicity includes the many causes of agitated delirium (Box 154-2). A thorough assessment of mental status, vital signs, and physical examination can help direct and narrow the differential diagnosis. Conditions that may be indistinguishable from cocaine toxicity include sedative-hypnotic withdrawal, toxicity from amphetamines and amphetamine derivatives, and heatstroke. Phencyclidine toxicity may be distinguished by the presence of multidirectional nystagmus, but the treatment is similar. Patients with anticholinergic poisoning typically have urinary retention, dry skin, and minimally reactive pupils as distinguishing factors. Infection should be considered in all hyperthermic patients.

MANAGEMENT

A severely poisoned patient is combative and unable to cooperate in assessment of vital signs. Actions taken during these first stages of the encounter are crucial (Box 154-3). Because the cause of the patient's state often is not clear, the initial priority is to recognize and treat the life-threatening agitated delirium.

Patients may transiently require physical restraints for complete vital signs to be obtained and intravenous access to be secured. If

Box 154-2 Differential Diagnosis of Agitated Delirium

- Metabolic causes
  - Electrolyte abnormalities
  - Hypoglycemia
  - Hypoxia
  - Uremia, hyperammonemia
- Structural lesions of the CNS
  - Trauma
  - Stroke
  - Hemorrhage
  - Mass
- Endocrine disease
  - Thyrotoxicosis
- Infections
  - Bacterial or viral meningitis or encephalitis
- Toxicologic causes
  - Sympathomimetics, stimulants
    - Cocaine
    - Amphetamines and derivatives
    - Caffeine
    - Phencyclidine, ketamine
  - Anticholinergics
    - Serotonin syndrome
    - Sedative-hypnotic withdrawal
- Heatstroke
- Postictal state

CNS, central nervous system.

Box 154-3 Initial Evaluation of Patients with Sympathetic Stimulation

- Rapid assessment of vital signs, especially core temperature
- Rule out hypoxia, hypoglycemia
- Pharmacologic sedation with benzodiazepines
- Electrocardiogram
- Urinalysis
- Serum creatine kinase

a chest restraint is used, a mesh vest is preferred to a jacket to help limit hyperthermia. The patient should have assessment with a bedside blood glucose monitor. Immediate pharmacologic sedation with intramuscular (IM) or intravenous (IV) administration of benzodiazepines may be necessary (see next section), which, in adequate doses, restores inhibitory tone to the CNS and decreases excessive sympathetic outflow to peripheral tissues. Sedation also facilitates measurement of vital signs (particularly core temperature), continuous electrocardiographic monitoring, and completion of the physical examination.

Pharmacologic Sedation

In adults, diazepam can be administered intravenously in increments of 10 mg every 5 minutes until sedation is achieved. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Persistently increased motor tone reflects an inadequate diazepam dose, even if the patient appears sleepy. In wildly agitated patients in whom 20 to 30 mg of diazepam has no notable effect, diazepam dosing may be increased by 10 mg with each subsequent dose with close monitoring until adequate sedation is achieved. For a patient in whom intravenous access is not possible because of agitation, IM midazolam 10 mg can be administered to facilitate subsequent interventions. Benzodiazepines also treat the choreoathetoid movements of crack dancing. Most cocaine toxic patients have salt and water depletion and require vigorous intravenous crystalloid replacement. If the cause of delirium is unclear, careful attention to the patient's respiratory status avoids the respiratory depression caused by excessive benzodiazepine administration in the presence of other sedative-hypnotic agents, such as ethanol.

Phenothiazines, droperidol, and haloperidol have a rapid onset with intramuscular injection, and CNS sedation is achieved. However, the anticholinergic effects of these agents can theoretically limit cooling by impeding diaphoresis, and they may also have associated dysrhythmic effects that theoretically may be additive to cocaine, and so benzodiazepines are preferred.

Box 154-4 Management of Stimulant-Induced Hyperthermia

- Early identification of elevated core temperature
- Large-bore intravenous access with rapid infusion of crystalloid
- Sedation and muscle relaxation with benzodiazepines
- Rapid cooling within 20 minutes*
- Foley catheterization to monitor output
- Laboratory analysis for organ function
  - Serum chemistries, creatinine, CK
  - Liver function
  - PT, PTT, fibrin split products
  - Bacterial cultures†
- Urinalysis for myoglobinuria
- Paralysis and intubation if necessary

CK, creatine kinase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
*Ideally with ice water immersion.
†Consider lumbar puncture or antibiotic therapy, especially in injection drug users.

Hyperthermia

Cocaine-induced hyperthermia must be treated with rapid cooling (Box 154-4). Patients who sustain elevated core temperatures above 106° F (41° C) for more than 20 minutes are likely to stabilize transiently and subsequently have fatal multisystem organ failure, often heralded by disseminated intravascular coagulation. Patients should have continuous monitoring of core temperature with a rectal probe. Heat generated by agitation and increased muscle tone can be terminated by aggressive use of benzodiazepines, with neuromuscular paralysis and intubation as required. Succinylcholine is relatively contraindicated because of hyperthermia and muscle breakdown, and its shared metabolism (plasma cholinesterase) with cocaine is likely to prolong the effects of both drugs. It is crucial to reduce core temperature to 102° F (38.8° C) within 20 minutes. Cooling blankets are insufficient. Ice water, wet sheets with large fans, and packing of the entire body in ice with continuous monitoring of core temperature can be used. These patients often require aggressive fluid resuscitation.[45]

Hypertensive Emergencies

The goal in hypertensive emergencies is to promptly reverse the vasoconstriction of norepinephrine at peripheral alpha-adrenergic receptors. Benzodiazepines restore the CNS inhibitory tone on the peripheral nervous system. With evidence of end-organ damage, intravenous nitroglycerin can be used.[46] Phentolamine, a direct alpha-adrenergic antagonist, is the antihypertensive of choice. It can be titrated slowly by repeated intravenous doses of 1 mg every 3 minutes with blood pressure monitoring. If adequate reduction in therapy by at least two thirds of mean arterial pressure is not achieved after two doses, phentolamine dose can be escalated by 1 mg every 3 minutes up to 5 mg/dose until adequate vasomotor control is achieved. Phentolamine effect will last roughly 45 minutes. Other antihypertensives that can be used

include hydralazine and short-acting intravenous calcium channel antagonists (see Chapter 84). Data for ideal vasodilators in this setting are lacking. In contrast to chronic hypertension, individuals with acute cocaine hypertension often have a normal blood pressure in the absence of the drug, and unless the patient's history suggests otherwise, a normal systolic and diastolic blood pressure should be the endpoint of therapy.

Beta-adrenergic antagonists may cause paradoxical hypertension with cocaine.[47,48] Patients undergoing cardiac catheterization show decreased coronary artery diameter in the presence of cocaine and beta-adrenergic antagonists.[48,49] The use of beta-adrenergic antagonists in cocaine toxicity or cocaine-related chest pain syndromes should be avoided while their role is investigated.[50-52] The treatment of cocaine-induced subarachnoid hemorrhage, MI, or aortic dissection differs from treatment of other causes of the same conditions. The combined use of phentolamine and beta-adrenergic antagonists may result in profound hypotension and is inadequately investigated. Likewise, data on the use of labetalol are disappointing. Because 1-year outcomes in younger low-risk patients presenting with chest pain are generally good,[53,54] the benefits attributed to beta-adrenergic antagonists in older patients with documented coronary artery disease may not be comparable. The 2008 American Heart Association guidelines consider beta-adrenergic antagonists potentially harmful and advise against their routine use.[52]

Dysrhythmias

Dysrhythmias from cocaine may be atrial or ventricular. Atrial fibrillation and supraventricular tachycardias are likely to be due to sympathetic stimulation and often respond to benzodiazepines. Beta-adrenergic antagonists should be avoided. Calcium channel blockers can be used if rapid atrial rhythms fail to respond to sedation, cooling, and volume resuscitation.

Important considerations in the differential diagnosis of a wide-complex tachycardia include hyperkalemia, direct sodium channel blockade, and ischemic ventricular dysrhythmia. In cocaine body packers or patients presenting with cocaine-induced adrenergic toxidrome, abrupt development of a wide-complex tachycardia with a pulse should be treated with empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus, with closely recorded cardiac monitoring to observe for QRS narrowing. If the patient does not respond with both QRS narrowing and hemodynamic stabilization, treatment by advanced cardiac life support should be instituted. Data regarding the ideal antidysrhythmic agent in this setting are limited. Fluid and electrolytes should be assessed and corrected as indicated. Close monitoring is required for patients with a Brugada-type conduction pattern.[26,27]

Cocaine-Related Chest Pain

The causes of cocaine-related chest pain are diverse (Box 154-5). A chest radiograph may identify aspirated foreign bodies or pneumothorax or pneumomediastinum from inhalational barotrauma. Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction,[55,56] or endocarditis with septic pulmonary emboli in intravenous drug abuse.

Cocaine acutely induces coronary vasoconstriction while increasing myocardial oxygen demand. Platelet aggregation is enhanced through thrombogenic and antifibrinolytic pathways.[57] These cumulative effects can result in coronary insufficiency. Cigarette smoking acutely exacerbates these conditions. Chronic cocaine use may accelerate atherogenesis and induce left ventricular hypertrophy. All of these factors contribute to myocardial ischemia or infarction. Of nonfatal MIs in patients aged 18 to 45 years, 25% were attributed to cocaine, even after adjustment of other known cardiac risk factors.[58]

Box 154-5 Causes of Stimulant-Induced Chest Pain

- Noncardiac
  - Pneumothorax
  - Pneumomediastinum
  - Pneumopericardium
  - Aortic dissection
  - Pulmonary infarction
  - Infection
- Foreign body aspiration
- Cardiac chest pain
  - Endocarditis
  - Pericarditis
  - Left ventricular apical ballooning
  - Ischemia, infarction
    - During acute intoxication
    - After acute intoxication
- Coronary stent thrombosis

Identification of a patient with a cocaine-related coronary syndrome is difficult. Patients may present hours to days after use, possibly because of vasoactive metabolites.[59] The patient may deny drug use and have atypical chest pain. Almost one third of cocaine-using patients with elevated serum enzymes have pleuritic chest pain.[60] There are no clear predictors for patients at risk because age, route of drug use, time to presentation, and preexisting risk factors for coronary artery disease are inadequate to identify patients sustaining MI.[60] In the setting of cocaine-related chest pain, risk stratification by TIMI score may not adequately identify patients at risk for 30-day adverse outcomes.[61] However, cocaine history alone in low-risk, asymptomatic patients assessed by coronary CTA was not associated with increased risk of coronary artery disease.[43] Patients with positive serum enzymes for MI often have significant angiographic stenosis.[41] Of patients without positive serum markers, 18% have significant disease by angiography.[41] Other predictors of significant disease in this group included elevated cholesterol concentration and prior diagnosis of coronary disease or MI.[41] Patients with previous coronary stent placement are at a high risk of thrombosis with cocaine use.[62]

As for most complications of cocaine use, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early.[63] Aspirin and nitrates should be administered.[57,59] In patients meeting electrocardiographic criteria for MI with persistent chest pain and hypertension and a clear history of acute cocaine intoxication, coronary vasodilation with intravenous phentolamine (1 mg) can be given slowly during 3 minutes. This dose can be repeated, if needed, as long as the patient's blood pressure remains stable. Morphine sulfate can be used to treat pain.[64] Patients with persistent chest pain and ST segments strongly suggestive of MI can be considered for percutaneous intervention or thrombolytic therapy, assuming there are no contraindications, such as uncontrolled severe hypertension.

In contrast to non–cocaine-induced myocardial ischemia or infarction, beta-adrenergic antagonists, including labetalol, are contraindicated during acute cocaine toxicity because coronary vasoconstriction may worsen.[47-51] In patients with cocaine-related coronary syndromes who are not acutely toxic, alpha-adrenergic vasoactive metabolites may be responsible. Administration of beta-adrenergic antagonists on discharge is controversial, especially if cocaine use is likely to continue, and we advise against this practice.[50,51,53,65-67] Heparin can be given, but fibrinolytic therapy is not well studied. Some mechanisms of cocaine-induced MI would be expected to respond to fibrinolytic agents. Patients failing to respond to vigorous treatment with nitrates and phentolamine who have known coronary artery disease or a previous ECG

confirming new ST segment elevations are candidates for cardiac catheterization or fibrinolysis if necessary. The same contraindications apply as for non–cocaine-induced MI. Nuclear imaging studies also may provide more diagnostic information.[18,38,54]

Antiplatelet and glycoprotein IIb/IIIa inhibitors and calcium channel antagonists seem to be of benefit to some patients with MI or ischemia of atherosclerotic origin. Theoretically, these agents may counter some of the platelet aggregation enhanced by cocaine, but data investigating their use are lacking. Patients with cocaine-related chest pain without other risk factors who have normal ECGs and cardiac enzymes are at low risk for MI. The role of provocative testing in these patients is not well established.[52]

In summary, cocaine-induced coronary ischemia is managed with vasodilators and benzodiazepines and avoidance of beta-adrenergic antagonists. In cooperative patients, aspirin, heparin, antiplatelet agents and calcium channel blockers, and interventional therapy can be used as they might be in patients with ischemic chest pain.

Interventions to cease cocaine use are warranted. For patients with documented coronary artery disease, cessation of cocaine use is imperative. Cocaine users presenting with chest pain who continued cocaine use after ED discharge were more likely to have recurrent ED visits than were those who stopped.[53]

Cocaine Body Packers

Before crossing international borders, "body packers" ingest cocaine that has been wrapped tightly into condoms or other latex products and sometimes coated in wax. Each packet can contain approximately 10 g of cocaine, and packers may swallow as many as 150 packets.[22,68] On arrival at the patient's destination, a cathartic is taken to stimulate gastrointestinal passage of the contraband for subsequent delivery and distribution. Body packers are likely to know the exact number of packets they ingested but may be reluctant to share that information.

A body packer may present without symptoms to the ED. The body packer should be placed immediately on continuous cardiac monitoring, with large-bore intravenous access. Diagnosis is made by history. An abdominal radiograph may confirm foreign bodies but cannot be used to count packets because plain radiographs have limited sensitivity in detecting an isolated or small number of packets. When uncertainty persists, a contrast study is warranted.[22]

Body packing also is used to transport heroin and other illicit substances. Although heroin body packing rarely requires surgical intervention, an asymptomatic patient may refuse to identify the packet's contents. A urine toxicology screen may be useful because small quantities of drug may be ingested in swallowing of the contraband. Rupture of a single cocaine packet can result in death because each packet contains almost 10 times the lethal dose. These patients may die suddenly. All cocaine body packers should be admitted to a monitored setting and given nothing to eat or drink except decontamination medications. Patients with bowel obstruction or a leaking or poorly secured packet who become symptomatic satisfy absolute criteria for immediate surgical removal of packets. Because of the large quantity of pure drug in one packet, patients with packet leaks are likely to die without prompt intervention. When evidence of cocaine toxicity is manifested, rapid transportation to the operating room may be the only way to save these patients. Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration may be required en route.

It is reasonable to administer activated charcoal (1 g/kg body weight) to an asymptomatic body packer whose airway is intact. Whole-bowel irrigation with polyethylene glycol solution facilitates gastrointestinal passage of the packets and cleanses the bowel in the event of emergent transport to the operating room.[22] Subsequent contrast studies may be required to evaluate for remaining packets. Computed tomography and contrast abdominal radiography may fail to detect isolated packets that contain potentially fatal quantities of cocaine. Patients suggesting that they swallowed a larger number of packets than are passed or who refuse to reveal the number ingested can have continued bowel irrigation, observation, and repeated studies. Endoscopic retrieval is generally discouraged because of concern for packet rupture during the procedure, but it has been done on occasion.[22,69]

All packets passed in the stool, through endoscopic procedures, or in the operating room should be counted carefully and promptly given to law enforcement officials. When law enforcement is not yet involved, hospital legal counsel or risk management and the hospital ethics committee may be helpful in determining the disposition of the packets and ultimately of the patient when he or she is medically cleared.[22]

Body Stuffers

A "body stuffer" is an individual who attempts to conceal evidence of cocaine possession by swallowing the drug while being pursued by law enforcement officials. These ingestions are usually unplanned events with generally small quantities of drug that were initially intended for personal use. The drugs are often swallowed in poorly sealed vials or glassine packets that may not be evident on radiographs. In general, patients ingest nonlethal doses and are asymptomatic. Activated charcoal (1 g/kg) can absorb any potentially released drug. Monitoring and whole-bowel irrigation should be performed if the quantity ingested is of concern or if signs of toxicity develop.[70] Body stuffers rarely have fatal events, but these patients usually have symptoms in the first 8 hours.

Levamisole-Related Complications

Patients with agranulocytosis, vasculitis, or other dermatologic manifestations require supportive care, evaluation for other potential causes,[36] and abstinence from further levamisole exposure. Reporting to the local department of health or poison control center can help track these cases.[34]

DISPOSITION

Acutely toxic patients who need only observation or who respond quickly to sedation and do not have complications can be discharged after the acute intoxication resolves. These patients may be extremely lethargic from catecholamine depletion, and it is best to discharge them with a responsible adult. Patients may be open to drug counseling and referral while in the ED.

Patients with chest pain (Box 154-6) who are acutely toxic and who show dynamic changes on the ECG, dysrhythmias, or congestive heart failure and patients requiring vasodilators or reperfusion should be admitted. These patients require further evaluation

Box 154-6 Admission Criteria for Cocaine-Related Chest Pain

- Persistent chest pain
- Electrocardiographic changes
- Dysrhythmias or conduction abnormalities
- CHF, cardiogenic shock
- Elevated enzymes
- Requiring vasodilation
- Preexisting CAD or stent placement
- Multiple risk factors for CAD

CAD, coronary artery disease; *CHF,* congestive heart failure.

of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use.

The disposition of patients with chest pain who are not acutely toxic is less clear. Admission is warranted for patients with complications or electrocardiographic changes and patients requiring pharmacologic intervention with vasodilators. Other patients may be admitted for short-term observation to an ED observation unit or discharged, depending on the level of concern about underlying coronary artery disease.

Young patients who present after resolution of chest pain with normal and unchanging ECGs, no dysrhythmias, and few or no risks of coronary artery disease are likely to have a good outcome.[54] Complications such as congestive heart failure and ventricular dysrhythmias typically are manifested within the first 4 hours.[18] After a 12-hour monitored observation period, patients with a benign clinical course and negative serum enzyme markers can be discharged.[54,71]

Body packers need to be observed until all packets have passed. Ideally, these patients have had three packet-free stools, a reliable packet count consistent with the ingestion, and a normal contrast radiographic study.[22] Body stuffers who receive activated charcoal, have normal ECGs, and remain asymptomatic with normal vital signs after 6 to 8 hours of observation may be discharged.

OTHER STIMULANTS

Amphetamines

Amphetamines enhance release of catecholamines from presynaptic nerve terminals by altering the pH of presynaptic vesicles. Amphetamines are usually taken as pills but are occasionally crushed and injected. The subsequent CNS stimulation results in sympathomimetic effects nearly identical to those from cocaine but not with the same frequency or intensity (see Box 154-1). Patients are at risk for hyperthermia, hypertensive emergencies, dysrhythmias, myocardial ischemia, and hyperkalemia associated with rhabdomyolysis. In contrast to cocaine, amphetamines do not block sodium channels and only minimally affect presynaptic reuptake of catecholamines. Although urine drug screens can identify amphetamines, they are of little utility in treatment of a toxic patient. The management follows the same guidelines as for cocaine (see Box 154-3), although the duration of toxicity is longer for amphetamines.

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA, ecstasy, XTC, Adam) is a chemically modified amphetamine originally taken orally at all-night dance parties or "raves." Patients describe the euphoria allowing "closeness to others," so it is sometimes called the love drug. The molecular structure of MDMA confers some serotonergic properties that may account for the "shimmering" visual effects reported.

Along with the usual complications of amphetamines, MDMA can precipitate a life-threatening hyponatremia. MDMA or its metabolite may alter release of endogenous stores of vasopressin.[72] Although the exact mechanism is not understood, patients with MDMA-induced hyponatremia have concentrated urine samples with a relatively high urine sodium concentration, similar to the syndrome of inappropriate secretion of antidiuretic hormone. Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction. Urine can be tested for specific gravity, and a sample should be sent to the laboratory for electrolyte analysis and osmolality. Normal saline or other crystalloids may worsen the hyponatremia because these patients are likely to retain more free water than sodium. Their fluid intake should be restricted unless severe hypovolemia exists, and they should be treated with hypertonic saline for neurologic impairment. A newer treatment of hyponatremia includes vasopressin V_2-receptor antagonists,[73] but it has not been described for these patients. In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotoninergic neurons.[74] Other MDMA variants, such as 3,4-methylenedioxyethamphetamine (Eve), may cause similar complications (see Chapter 156).

Methamphetamine

Methamphetamine, known as crank and crystal meth, is a fat-soluble, smokable, designer amphetamine. Complications from methamphetamine use are similar to those from other sympathomimetics. The duration of action can be significantly longer, however, with some paranoid delusions persisting for 15 hours. The production of methamphetamines requires a variety of metal salts, and lead toxicity from inappropriately produced drug is reported.[75] Injuries during illicit methamphetamine production or police raids include exposure to anhydrous ammonia, hydrochloric acid, sodium hydroxide, ether, and ephedrine as well as burns and explosions.

Ephedrine and Ephedra

Ephedrine is another illicitly used amphetamine-like agent associated with complications of excessive sympathomimetic stimulation. Ephedra, a plant-derived product, also known as a Chinese herbal product, ma huang, has been associated with strokes and deaths in adolescent users.[76] The U.S. Food and Drug Administration has banned all ephedra-containing dietary supplements.

Khat and Methcathinone

Khat is a stimulant agent naturally occurring in the leaves of the plant *Catha edulis*.[77] These leaves are chewed to extract the active compounds, cathinone and methcathinone, which are stimulants with sympathomimetic effects.[78] Management and disposition follow the same guidelines as for cocaine. Smoking of khat does not typically result in clinical effects because the agent degrades with pyrolysis. Illicitly manufactured methcathinone is known as cat. Some methcathinone users experienced an extrapyramidal syndrome associated with elevated manganese levels, probably resulting from an inadvertent contaminant during production or inadequate purification. The role of chelation therapy for elevated manganese levels is uncertain.[79]

Other Stimulants

Substances vended as bath salts and labeled "not for human consumption" contain similar substances, including the methcathinone derivative mephedrone and the cathinone derivative methylenedioxypyrovalerone. These are exploited for an adrenergic "high"[80,81] and have no pharmacologically approved medical indications in the United States. Treatment is identical to that of cocaine and amphetamine toxicity.

KEY CONCEPTS

- Rapid sedation with an intravenous benzodiazepine is the key for most symptoms from cocaine and other stimulants.
- Hyperthermia is a high-risk sign, and body temperature must be reduced rapidly.
- Beta-adrenergic blockade may cause paradoxical hypertension and increase coronary vasoconstriction and is contraindicated in acute toxicity.
- Wide-complex rhythms secondary to cocaine may respond to intravenous bicarbonate therapy.
- Cocaine body packers who become symptomatic need immediate surgery.
- Amphetamine symptoms and effects last longer than those produced by cocaine.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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