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Evaluating Sympathomimetic Intoxication in an Emergency Setting

ABSTRACT *Sympathomimetic-like drugs (ie, cocaine, amphetamines, and sympathomimetic amines) mimic the actions of the endogenous neurotransmitters that stimulate the sympathetic nervous system. The classic signs and symptoms (toxidrome) often seen with the sympathomimetic drugs include hyperactivity, mydriasis (dilated pupils), hypertension, tachycardia, and hyperthermia; some of these drugs also precipitate psychoses, hallucinations and seizures. Qualitative confirmation by the laboratory that the patient is experiencing a sympathomimetic drug reaction can be helpful to the clinician. However, some of the conventional toxicologic drug screens used by many clinical laboratories do not differentiate within a specific class of drugs (eg, amphetamine vs methamphetamine). Although a drug screen can help to confirm ingestion of a sympathomimetic drug, diagnosis and treatment are often based on history of use (often unreliable), physical examination, and the classic toxidrome observed with this class of drugs.*

This is the third article in a 3-part series on clinical toxicology and drugs of abuse. On completion of this series, the reader will be able to correlate clinical findings from the poisoned patient with data provided by the clinical laboratory that leads to a diagnosis and describe the therapeutic interventions used by clinicians for patient management.

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Case Presentation

The patient was a 28-year-old man in police custody arrested for illegal possession of drugs by customs agents in a Chicago airport who confessed to swallowing several "bags of coke" prior to boarding his plane in Colombia. The patient was agitated and complained of chest pain. His pupils were equal and reactive, lungs clear to auscultation, and skin diaphoretic and warm to touch, with no cyanosis or needle tracks. His pulse was 140 beats per minute; respiratory rate, 28 breaths per minute; blood pressure, 220/130 mm Hg; and temperature, 39.6°C (103.2°F). The patient's abdomen was soft and non-tender with normal bowel sounds. An electrocardiogram revealed a sinus tachycardia with large 5-mm ST segment elevation in the anterior leads, consistent with acute myocardial infarction. Otherwise, the patient was healthy and had no previous cardiac disease. The chest radiograph showed no infiltrates or pulmonary edema; a plain radiographic film of the abdominal area (kidney, ureter, and bladder) revealed multiple radio-opaque packets throughout the gastric and intestinal tract.

Suspecting ingestion of a sympathomimetic drug, the physician ordered the tests in Table 1 and then gave the patient large doses of benzodiazepines for sedation and nitroglycerin for chest pain. Because of the acute myocardial infarction, the cardiologist elected to give thrombolytics. However, because thrombolytics were administered, the general surgeon refused to perform an exploratory laparotomy and removal of the "cocaine packets" because of the increased risk of bleeding. The patient subsequently developed generalized seizure activity, worsening hyperthermia, rhabdomyolysis, and intracranial hemorrhage. He died 48 hours after admission.

The sympathomimetic amines and sympathomimetic-like drugs mimic the actions of the endogenous neurotransmitters that stimulate the sympathetic nervous system. Stimulation of the peripheral nervous system occurs via receptors (alpha or beta) on neurons that involve either adrenergic (epinephrine) or noradrenergic (norepinephrine) neurons.[1,2] Stimulation of the central nervous system (CNS) occurs via neurons that involve dopamine and serotonin receptors. Some of the sympathomimetic drugs act directly with receptors on the neurons of the sympathetic nervous system to elicit a pharmacologic response;

Table 1. Laboratory Results for Patient Suspected of Sympathomimetic Drug Ingestion

Test	Patient Result	Reference Range
Blood gases (room air)		
pH	7.34	7.35-7.45
P_{CO_2}, mm Hg	28	35-45
P_{O_2}, mm Hg	80	90-95
Electrolytes		
Sodium, mEq/L (mmol/L)	148 (148)	136-145 (136-145)
Potassium, mEq/L (mmol/L)	5.5 (5.5)	3.5-5.0 (3.5-5.0)
Chloride, mEq/L (mmol/L)	109 (109)	99-109 (99-109)
Bicarbonate, mEq/L (mmol/L)	20 (20)	22-28 (22-28)
Blood urea nitrogen, mg/dL (mmol/L)	32 (11.4)	10-20(3.6-7.1)
Creatinine, mg/dL (mmol/L)	1.1 (97)	0.6-1.2 (53-106)
Glucose, mg/dL (mmol/L)	180 (10.0)	70-105 (3.9-5.8)
Creatine Kinase, U/L (U/L)	2,300 (2300)	21-132
Troponin, ng/mL	100	< 2
CK-MB, ng/mL	300	< 5
CBC		
RBC count	5.4 M/μL (5.4 x 10^{12}/L)	4.7-6.1 M/μL (4.7-6.1 x 10^{12}/L)
WBC count	19.0 K/μL (19.0 x 10^{9}/L)	4.8-10.8 K/μL (4.8-10.8 x 10^{9}/L)
Hemoglobin	15.2 g/dL (152g/L)	14-18 g/dL (140-180 g/L)
Hematocrit	47% (0.47)	42%-52% (0.42-0.52)
Platelet count	320 K/μL (320 x 10^{9}/L)	150-400 K/μL (150-400 x 10^{9}/L)
Prothrombin time, s	20 (after thrombolytic therapy)	11-14
Partial thromboplastin time, s	60 (after thrombolytic therapy)	25-40
Urinalysis		
Blood	Positive	Negative
RBCs, per high-power field	0	0-2
WBCs, per high-power field	0	0-5
Ethanol, mg/dL (mmol/L)	< 5 (<1.1)	< 5 (<1.1)
Urine drug screen		
Amphetamines	None detected	None detected
Cannabinoids	None detected	None detected
Cocaine metabolite	Positive	None detected
Barbiturates	None detected	None detected
Opiates	None detected	None detected
Phencyclidine	None detected	None detected

others increase the release and/or block the reuptake of endogenous norepinephrine or use a combination of these mechanisms.

Naturally occurring sympathomimetic substances have been used by some cultures for centuries. Chinese physicians have used Ma-huang (ephedrine) derived from the *Ephedra* plant for more than 5,000 years. For 2,000 years the Incas of Peru during their religious ceremonies often chewed the leaves of the coca plant, *Erythroxylon coca*, to obtain the psychotropic effects of cocaine. Table 2 lists some common sympathomimetic drugs. Although some sympathomimetic drugs are commonly found in prescribed or over-the-counter medications, many are illicit drugs primarily abused for their stimulant, psychoactive, and hallucinogenic properties. Some of the more commonly abused compounds include cocaine, the sympathomimetic amines (ie, amphetamine, methamphetamine), the "designer" hallucinogenic amphetamines (ie, 3,4-methylenedioxymethamphetamine [MDMA], 3,4-methylenedioxyamphetamine [MDA], 3,4-methylenedioxyethamphetamine [MDEA]), and methcathinone.

Cocaine

Cocaine was first isolated from the coca plant by Albert Niemann, a graduate student of Carl Wohler (who synthesized urea). From the 1860s and throughout the turn of the century, cocaine appeared in various elixirs and tonics, including Vin Mariani (mixture of wine and cocaine) and the original Coca-Cola (then sold as a tonic and headache remedy). Cocaine became popular within the scientific community when Sigmund Freud published his famous treatise, *Über Coca*. By 1914, cocaine use was viewed as a social problem and classified (incorrectly) as a narcotic under the Harrison Act. It eventually became a Schedule II controlled substance under the Controlled Substance Act (Public Law 91-513) of 1970.

Cocaine is sold on the street in 2 forms: the hydrochloride salt and "crack." The purity of the hydrochloride salt varies (around 30%). The salt form is typically diluted or "cut" with other agents ,such as mannitol, lactose, sucrose, or other CNS stimulants, such as caffeine, phenolpropanolamine, ephedrine, lidocaine, amphetamine, heroin ("speedballs"), and even phencyclidine.[3] Cocaine is typically "snorted" through a straw (or "tooter") or from a "coke spoon" or "bullet." Free-basing is the process by which cocaine hydrochloride is purified by mixing with an aqueous base, followed by adding an organic solvent to extract the free form of the drug. This form is then evaporated to dryness, and the substance can then be smoked.

Crack, sold as the free-base form of cocaine, is also smoked. The name *crack* comes from its rock-like appearance and the crackling sound that is produced when it is smoked. Both *crack* and free-base cocaine are highly purified (85% to 90%). Cocaine can also be administered intranasally, orally, or intravenously ("mainlining"). When insufflated, the onset of action is within 20 to 30 minutes. Intravenous administration and smoking produce results within seconds; peak effects are noted within 3 to 5 minutes.

Cocaine (methylbenzoylecgonine), an ester of benzoic acid and the amino alcohol (methylecgonine), is primarily metabolized to benzoylecgonine (40%) and ecgonine methyl ester (30%-40%); norcocaine and ecgonine are minor metabolites (Fig 1). The conversion of cocaine to benzoylecgonine can occur by spontaneous hydrolysis at physiologic or alkaline pH[4] and/or be produced enzymatically by liver carboxylesterases.[5] Ecgonine methyl ester formation involves enzymatic hydrolysis by pseudocholinesterase, liver esterases, and, possibly, the specific enzyme, benzoylesterase.[5] Because plasma cholinesterase is a key determinant in the relative concentrations of the various metabolites of cocaine, patients with a pseudocholinesterase deficiency who use cocaine may be at greater risk for adverse reactions due to increased toxic effects.[5] Cocaine and norcocaine appear to be the major contributors to the cardiovascular and convulsant effects of cocaine.[6] Simultaneous ingestion of ethanol with cocaine forms the metabolite "cocaethylene" or "ethylcocaine,"[7] which has similar physiologic properties to cocaine, but enhances the euphoria and cardiotoxic effects.[8] The average half-life for cocaine is about 60 minutes and for ethylcocaine, about 120 minutes.

Elimination of cocaine and its metabolites is affected by their protein binding; benzoylecgonine is more protein-bound than cocaine. Although the urinary excretion rate of benzoylecgonine parallels cocaine, the metabolite resulting from its increased protein binding can typically be detected for at least 48 hours after cocaine use; in rare cases, it has been detected up to 3 weeks following substantial use.[9] On the average, 1% to 9% of the drug is excreted unchanged (depending upon the urine pH): 26% to 54% as benzoylecgonine; 18% to 41% as ecgonine methyl ester, and 2% to 3% as ecgonine.[5]

Cocaine blocks sodium channel conductance, causing an increase in the threshold needed to generate an action potential[5]; it also blocks the

Table 2. Common Sympathomimetic Agents

Amphetamines
Amphetamine (Dexedrine)
Methamphetamine (Desoxyn)
Phenylpropanolamine
Ephedrine
Pseudoephedrine
Phentermine
Fenfluramine and dexfenfluramine
Fenfluramine/phentermine ("Fen-Phen")
Designer amphetamines
3,4-methylenedioxyamphetamine (MDA, "love drug")
3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy; E; XTC; Adam; M&M")
3,4-methylenedioxyethamphetamine (MDEA, "Eve")
4-methyl-2,5-dimethoxyamphetamine (DOM, "STP; serenity; tranquility; peace")
4-bromo-2,5-dimethoxyamphetamine (DOB)
Methcathinone (Ephedrone, "Cat; Jeff")
Cocaine
Phencyclidine
Caffeine
Theophylline

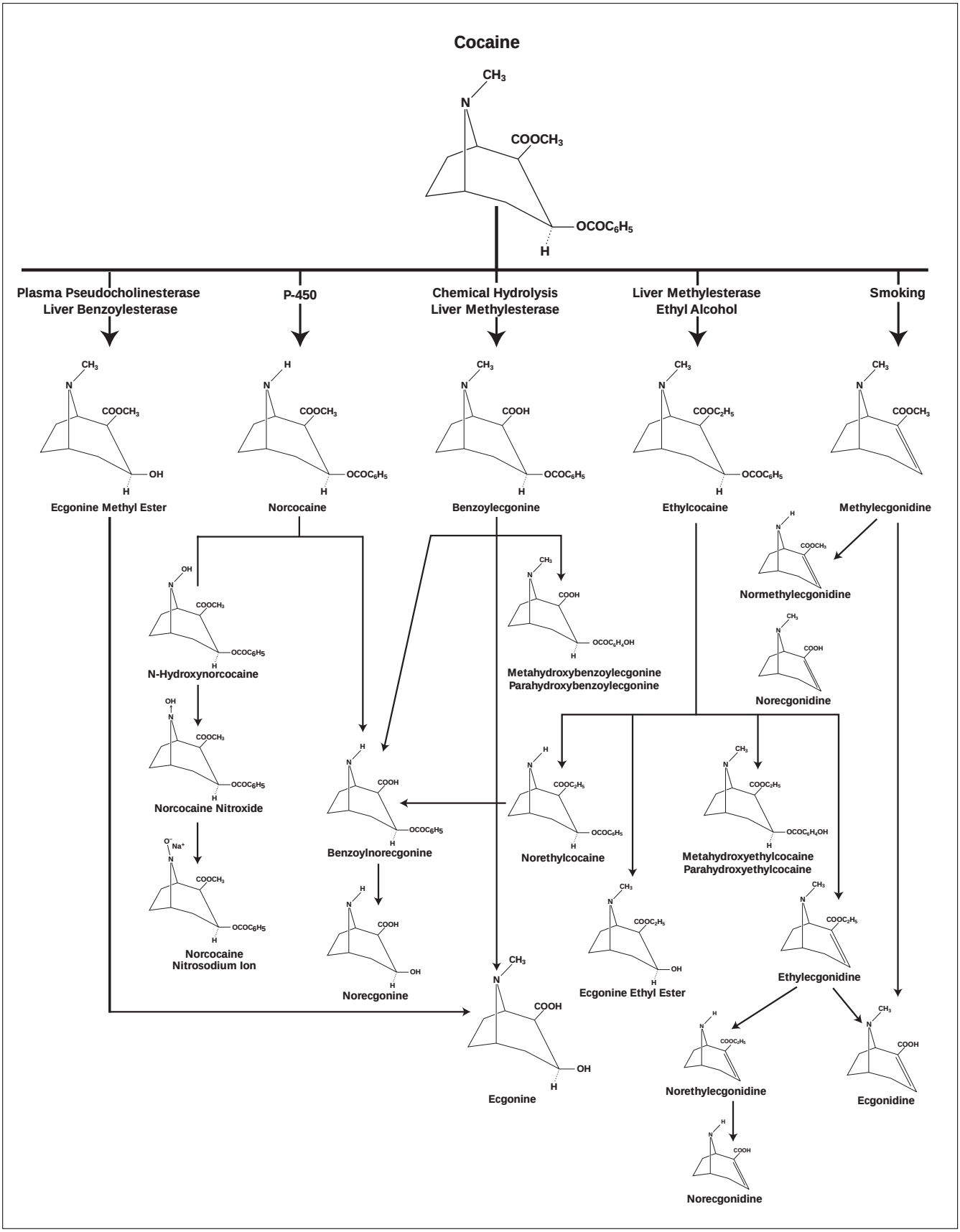


Fig 1. Pathways in the metabolism of cocaine. Adapted from Isenschmid DS. Cocaine. In: Levine B, ed. *Principles of Forensic Toxicology*. Washington, DC: AACC Press; 1999:227. Used by permission.

reuptake of neurotransmitters (norepinephrine, dopamine, and serotonin). The effect of cocaine on serotonin release has been implicated in the depression and craving observed after cocaine withdrawal (which usually diminishes in 1-3 weeks). The increase in norepinephrine is responsible for the classic adrenergic effects (mydriasis, vasoconstriction, hypertension, tachycardia, tachypnea) seen with cocaine use.[5] The behavioral changes appear to be related to the effect of cocaine on dopamine. Intense euphoria, psychic energy, heightened sexual excitement, and self-confidence are desirable effects sought by cocaine users; undesirable effects include paranoia, hallucinations, and dysphoria. CNS stimulation ("rush") followed by depression ("crash") is the driving force that results in long-term abuse of cocaine. A syndrome known as *cocaine-excited delirium* is characterized by hyperthermia, delirium, agitation, and cardiac and respiratory arrest.[5]

Cocaine intoxication produces neurologic effects, hyperthermia, and complications related to the heart, lungs, skeletal muscle, and vascular system. Cocaine causes an increase in psychomotor activity, thus augmenting heat production, and an increase in systemic hypertension and platelet aggregation.[10] Tachycardia is common, although with low doses of cocaine, bradycardia can occur. Myocardial ischemia and infarction can occur regardless of the route of administration and under conditions of withdrawal.[11] Patients with cocaine-associated myocardial infarction frequently have atypical chest pain or chest pain delayed for hours to days after their most recent use of cocaine. Cocaine-induced chest pain typically is accompanied by an abnormal electrocardiogram (Fig 2) with ST-segment elevation and T-wave inversion. Q-wave and non-Q-wave infarctions occur with equal frequency.[12] A broad spectrum of pulmonary complications can occur with cocaine use, for example, noncardiogenic pulmonary edema or pneumothorax.[13] Cocaine use can also cause severe rhabdomyolysis with substantial increases in creatine kinase levels, profound hypotension, and hyperthermia. Acute renal failure may result from both myoglobinuria and renal ischemia.[14] Maternal use of cocaine has an adverse effect on fetal growth and development; deliveries of premature infants are common.[15] Symptoms of neonatal cocaine withdrawal usually begin within 24 to 48 hours of birth.

Cocaine intoxication can also result from patients swallowing containers, multilayered condoms, latex balloons, or packages filled with illicit drugs such as cocaine. People who swallow illegal contraband and drugs for the purposes of smuggling across international borders are called "body packers."[11] Patients who swallow drugs, attempting to conceal the evidence to avoid being arrested, are called "body stuffers" (Fig 3).[11] Because of faulty wrapping technique, body stuffers are at greater risk for life-threatening toxic effects.

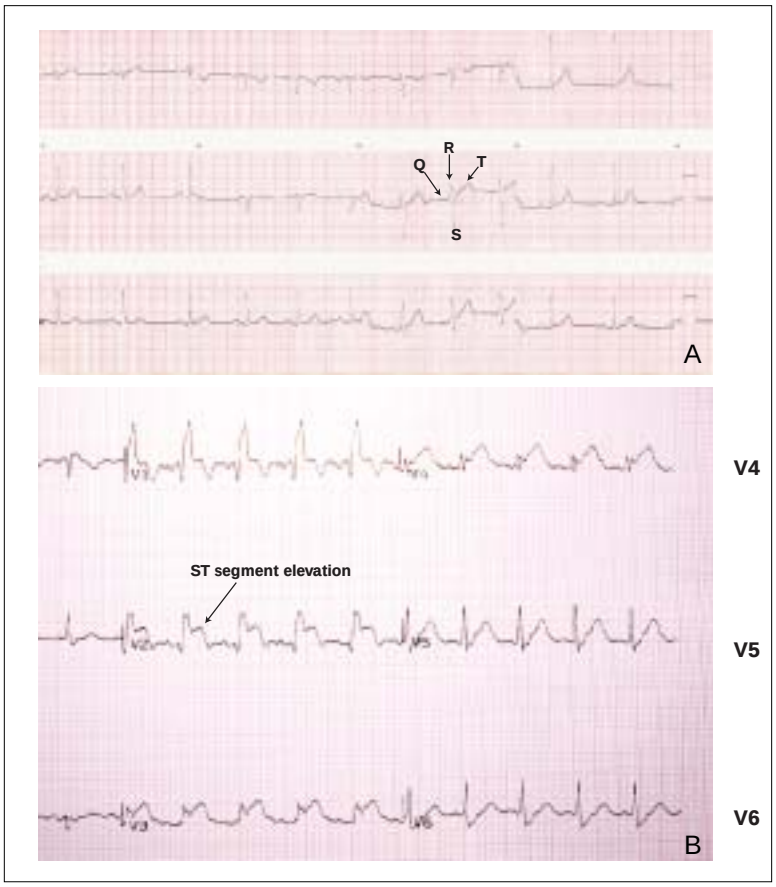


Fig 2A, An electrocardiogram demonstrating normal sinus rhythm with no evidence of cardiac ischemia or myocardial infarction. Fig 2B, ECG demonstrating sinus tachycardia and profound ST segment elevation in the anterior leads consistent with an acute myocardial infarction.

Sympathomimetic Amines and Amphetamines

Sympathomimetic amines, which are stimulants with alpha- and beta-adrenergic effects, are chemically related to beta-phenylethylamine (the core structure for catecholamines). Substitutions at different positions of the beta-phenylethylamine structure are possible and result in different amphetamine-like compounds, often referred to as amphetamines or amphetamine analogs.[2] Compounds with a methyl substitution at the alpha carbon, such as amphetamine and methamphetamine, possess strong stimulant, cardiovascular, and anorexic activity[16]; large group substitutions at the alpha carbon reduce the stimulant and cardiovascular activity but retain the anorexic properties.[17] Renal elimination of the sympathomimetic amines is highly dependent

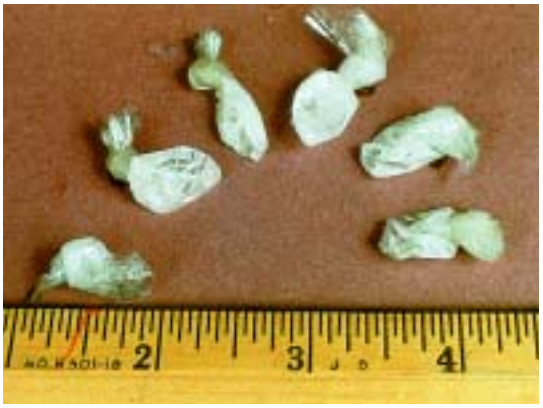


Fig 3. Cocaine packets obtained from body stuffer.

upon the urinary pH: urine acidification (pH <5.6) decreases the plasma half-life; urine alkalization increases the plasma half-life.[18]

Amphetamine and Methamphetamine

Amphetamines were first synthesized in 1877 and were used clinically during the 1930s as CNS stimulants for treatment of narcolepsy and depression. During the 1940s and early 1950s, amphetamine use attained epidemic proportions owing to its increased use by soldiers, factory workers, and prisoners of war in Japan during World War II. From the 1950s to the 1970s, methamphetamine abuse became a social problem in the United States[19] and became a favorite drug among members of West Coast motorcycle gangs. Methamphetamine was and sometimes still is referred to as "speed," "go," or "crank" (from the illicit transportation of the drug using motorcycle crankcases). Owing to increased abuse of both of these drugs, they are now classified as Schedule II controlled substances. Methamphetamine, which is easily synthesized, is the most illicitly produced controlled substance in the United States and is widely abused in the Pacific Coast states, Hawaii, and Pacific Rim countries such as Japan and Korea.[20]

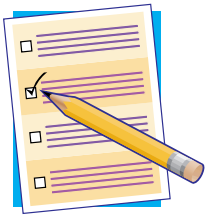
Amphetamine and methamphetamine exist as *d* (dextro) and *l* (levo) isomers, but only the *d* isomer of amphetamine (3 - 4 times more potent than the *l* isomer to the CNS), is used therapeutically. The pharmacologic profile of methamphetamine is similar to amphetamine, except its effects on the CNS are more substantial.[21] Amphetamine and methamphetamine facilitate the release of catecholamines, particularly dopamine and norepinephrine, from the presynaptic nerve terminals,[22] block the reuptake of catecholamines by competitive inhibition,[2] and, at higher doses, cause the release of serotonin (5-hydroxytryptamine) and affect central serotonin receptors. Stimulation of the sympathetic nervous system by amphetamine and methamphetamine causes tachycardia, hypertension, visual and tactile hallucinations, mydriasis, diaphoresis, and hyperthermia.[23]

Liver biotransformation as the major route of amphetamine elimination gives rise to a number of biologically active, ephedrine derivatives.[24] Amphetamine is also one of the active metabolites of methamphetamine (Fig 4). A significant portion of the sympathomimetic amines is excreted via the kidneys: amphetamine (30%) and methamphetamine (40%-50%).[18,24] In the United States, amphetamine and methamphetamine drugs are currently prescribed for narcolepsy, attention-deficit hyperactivity disorder, and short-term weight reduction for the treatment of exogenous obesity.[2] A pure large crystalline form of methamphetamine, called "ice," can be smoked, ground and insufflated, or dissolved and administered parentally.[25]

Designer Hallucinogenic Amphetamines (MDMA, MDA, MDEA)

Two of the oldest so-called designer group of sympathomimetic drugs, MDMA and its *N*-demethyl metabolite, MDA are derivatives of methamphetamine and amphetamine, respectively. MDMA and MDA have been synthesized as appetite suppressants, antitussives, ataractics, and anorexiants and as an adjunct to enhance psychotherapy.[26] MDA, widely abused in the 1960s and 1970s, was always considered an illicit drug in the United States. Use of MDMA increased in popularity in the 1980s. Due to its increased abuse potential and hallucinogenic and psychoactive properties, it became a Schedule I controlled substance on July 1, 1985. The drug has become popular among young adults at nightclubs, rock concerts, and, recently, at late-night parties called "raves" in England, Australia, and the United States.[27,28]

The designer hallucinogenic amphetamines (Table 2), have variable pharmacologic effects, especially if taken in high doses. MDA and MDMA exist as isomers: the S (+) isomer of MDA is more amphetamine-like; the R (–) isomer is hallucinogenic. Both isomers of MDMA act as mild hallucinogens. Stimulation of the CNS by MDMA is about one tenth that of amphetamine. Unlike amphetamine and methamphetamine, MDMA is a potent releaser of serotonin.[29] In an overdose setting, it can produce behavioral changes, seizures, dysrhythmias, hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation, in addition to the classic amphetamine-like effects of vasoconstriction, tachycardia, and mydriasis.[30] MDA and other related designer amphetamines, such as MDEA (or



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"Eve"), have similar clinical effects in acute and chronic intoxication. Users of MDMA indicate that the drug enhances pleasure, heightens sexuality, and expands consciousness without loss of control.[30]

Methcathinone (Cat) and Khat

Khat, the fresh leaves of the *Catha edulis* plant, is one of the most commonly used drugs in eastern and central Africa and the Arabian Peninsula. It is also known as "quat" and "gat." The leaves can be chewed or brewed as a tea. Khat causes increased alertness, insomnia, euphoria, anxiety, and hyperactivity. Cathinone is the primary psychoactive compound in the plant.[31] Methcathinone (also known as "cat" or "Jeff" on the streets) is the methyl derivative of cathinone and can be synthesized from ephedrine. The drug is widely abused in Russia. Use of the drug in the United States was first reported in Michigan in the early 1990s; however, recently its use has been noted in other states as well.[32]

Diagnosis of Sympathomimetic Intoxication

Table 3 lists the common clinical and laboratory findings associated with sympathomimetic intoxication. Diagnosis of a specific sympathomimetic intoxication is often difficult, because the signs and symptoms are similar to an amphetamine or a cocaine overdose. Typically the patient presents to the emergency department in an agitated state and with sinus tachycardia and hypertension. Also, at high doses, these sympathomimetic drugs can induce seizures, hyperthermia, and rhabdomyolysis. Rhabdomyolysis usually results from agitation and hyperthermia.[33] Mydriasis (dilated pupils) is a common sign observed with amphetamine and cocaine intoxication. Another common finding with the sympathomimetic drugs is diaphoresis; hyperkalemia and metabolic acidosis are also usually present.

Patient Management

Table 4 lists the overall approach to managing a patient suspected of sympathomimetic intoxication. Protecting the patient from hypoxia, and cardiac ischemia is critical.[11,32] The patient should be given intravenous hydration and therapy in addition to being placed on a cardiac monitor. Nitroglycerin can be used to treat ischemic chest pain and hypertension. Nitroprusside can be given for refractory hypertension. The control of the patient's hyperthermia is best achieved by rapid cooling with mist spray fans and/or an ice bath. Patients with substantial elevation of creatine kinase or myoglobinuria (due to rhabdomyolysis) require vigorous hydration to maintain a urine output of at least 3 mL/kg per hour; mannitol for forced diuresis; sodium bicarbonate to alkalinize the urine; and hemodialysis if renal failure occurs.[34]

Although gastric suction may be used if the patient is seen early after ingestion (Table 4), activated charcoal seems to be the safest and most effective way to remove drug from the stomach. Whole bowel irrigation may also be required, especially with drug intoxications seen with body packers and stuffers.[11] Benzodiazepines can be

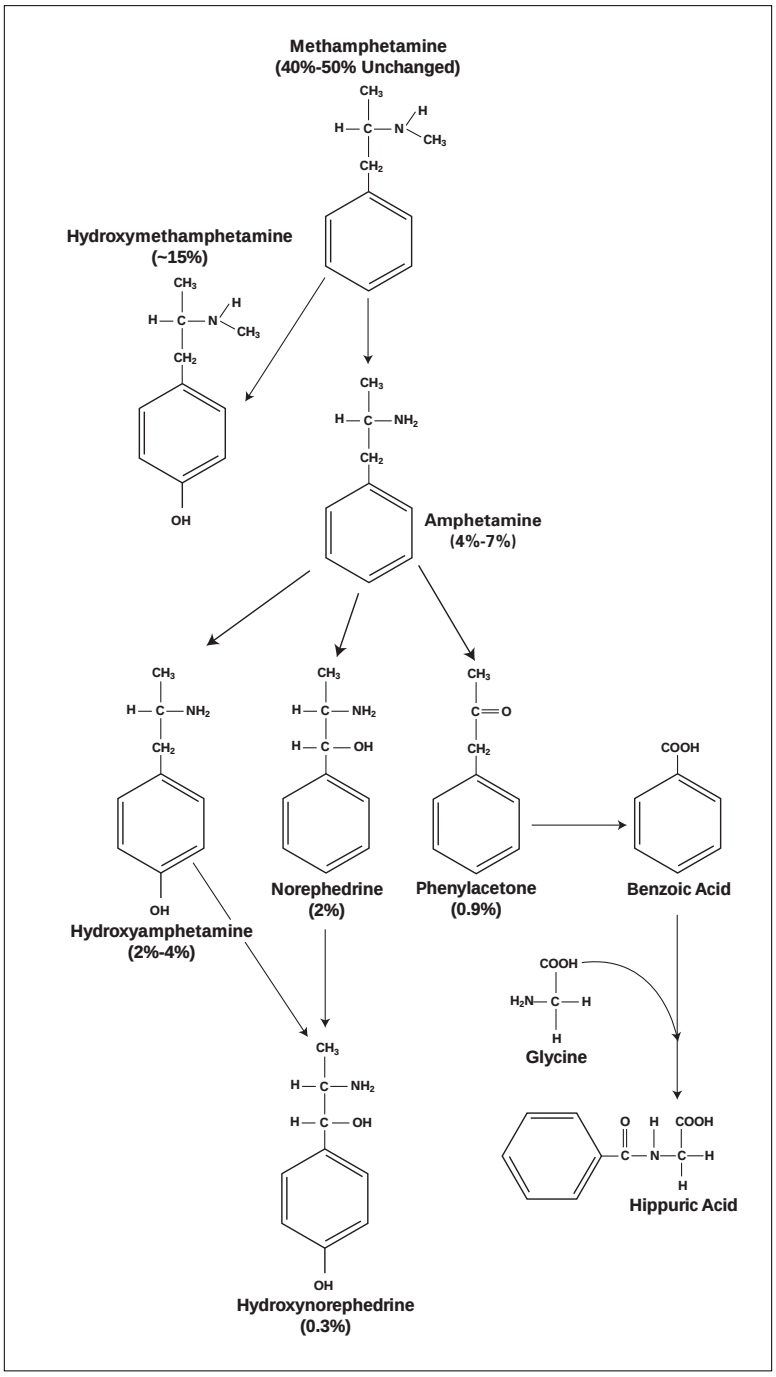

Fig 4. Metabolism of methamphetamine. Moore K. Amphetamines/sympathomimetic amines. In: Levine B, ed. *Principles of Forensic Toxicology*. Washington, DC: AACC Press; 1999:269. Used by permission.

Table 3. Clinical and Laboratory Findings Associated With Sympathomimetic Intoxication

Central nervous system
Anxiety and agitation
Hallucinations and seizures
Hyperthermia
Coma
Death
Cardiovascular
Sinus tachycardia
Hypertension (systolic and diastolic)
Cardiac-associated chest pain
Pulmonary
Tachypnea, irregular respiratory pattern
Ophthalmic
Mydriasis (dilated pupils)
Skin and extremities
Diaphoresis (sweaty skin)
Flushing
Muscle
Rhabdomyolysis and myoglobinuria
Laboratory
Leukocytosis
Hyperkalemia
Metabolic acidosis
Elevated muscle enzymes (creatine kinase [CK], lactate dehydrogenase, aspartate transaminase)
Elevated cardiac markers (troponin, CK-MB)
Ketonuria
Myoglobinuria
Increased blood urea nitrogen and creatinine levels

used for sedation, have good anticonvulsant activity, and can be effective for the treatment of delirium induced by cocaine and amphetamines.[32] Thrombolytic agents can also be used but should be reserved for patients who are clearly having an acute myocardial infarction, cannot undergo invasive reperfusion, fail to respond to vasodilator therapy, and have low risk for an intracranial bleeding episode.[35]

Laboratory Evaluation of Sympathomimetic Intoxication

Clinical Tests to Assess Sympathomimetic Abuse

Common tests requested by clinicians for patients suspected of sympathomimetic overdose include blood gases, electrolytes, glucose, renal and liver function tests, creatine kinase, coagulation studies (such as prothrombin time and partial thromboplastin time), a CBC, and urinalysis. Cardiac markers are also helpful to confirm myocardial infarction, especially measurement of troponin levels.[11,32] Radiographs of the chest (pulmonary edema or infarction, pneumothorax) and abdominal area should also be performed.[11,32] The abdominal radiographic film (kidney, ureter, and bladder) is especially helpful in cocaine overdoses to detect the presence of cocaine contraband or packets. Electroencephalogram and computed tomography of the head may also be necessary to assess the impact of the drug on the brain and intracranial bleeding.

Detection of Abused Sympathomimetics Drugs

There are several automated and point-of-care immunochemical methods and chromatographic techniques, such as thin layer chromatography, high-performance liquid chromatography, gas chromatography, and gas chromatography–mass spectrometry (GC-MS), that are available to detect and determine levels of sympathomimetic drugs. Determination of plasma or serum levels of any of the sympathomimetic drugs is of little value, because drug levels do not correlate well with the severity of the intoxication.[11,32] Thus, the most common approach in the emergency setting is to use rapid immunoassays for qualitative screening of the patient's urine. Many immunoassay techniques are available for the detection of amphetamines and cocaine metabolite. The cross-reactivity of the antibodies in these systems determines the specificity of the assay and may vary with different antibody lots. Although urine drug screens in the acute setting for cocaine are fairly reliable, the amphetamine urine drug screen is of little value owing to a large number of false-positive and false-negative results. For this reason, many physicians request confirmation of a positive amphetamine urine drug screen. However, a positive drug screen and confirmation for any of the sympathomimetic drugs only implies use of the drug and cannot be correlated to impairment.

The Substance Abuse and Mental Health Services Administration (SAMHSA) regulates drug testing in the workplace for the federal government. Although immunoassay antibodies for workplace testing are ideally designed to detect only the drugs regulated by the federal government, in the clinical setting it is desirable for these antibodies to detect (cross-react with) parent compounds and pharmacologically active metabolites. The manufacturer lists immunoassay cross-reactivity information in its product insert. However, sometimes these cross-reactivity studies use lower concentrations of potentially interfering substances than encountered in the clinical setting (patient's drug concentration is considerably

higher). Even though parent compounds may be shown not to cross-react in an immunoassay, it is possible for endogenous metabolites (which are often not tested by the manufacturer) to interfere with the assay. Table 5 lists some compounds that can potentially interfere with the analysis of amphetamines and cocaine metabolites.

Unlike drug testing in the clinical setting, regulated workplace drug testing requires initial testing by immunoassay and confirmation of "presumptive" positive drug screens by GC-MS. Immunoassays are designed with a cutoff concentration mandated for federally regulated testing. However, the predetermined cutoff concentration may not be appropriate in clinical settings; thus, the laboratory may choose to use different criteria. Although confirmation is not required for clinical testing, confirmation by a second method may be necessary to accurately identify the drug causing the initial or presumptive positive test or to deal with cases seen in the emergency setting that involve employee or workplace testing, worker's compensation, and potential litigation. In these situations, confirmation of a presumptive positive drug screen should also be performed by GC-MS.

Cocaine

Immunoassays used to detect cocaine abuse are designed to primarily measure benzoylecgonine, a major metabolite, although cocaine and/or other metabolites can be detected to varying degrees. SAMHSA requires a cutoff of 300 ng/mL for screening and a cutoff of 150 ng/mL for the confirmation of cocaine (as benzoylecgonine) by GC-MS.[5]

Meconium, the first stool specimen of the neonate, is the specimen of choice for detecting fetal cocaine exposure due to maternal use. Approximately 12 to 16 weeks after conception meconium begins to form in the fetal intestines; cocaine has been detected as early as 17 weeks of gestation in the meconium of an aborted fetus.[36] A substantial portion of the immunoreactivity in meconium samples is due to the cocaine metabolites *m*-hydroxybenzoylecgonine and *p*-hydroxybenzoylecgonine.[37] Most current immunoassays exhibit cross-reactivity with these metabolites, which is important to the laboratory performing meconium testing. If results are to be confirmed by GC-MS for medical and/or legal reasons (eg, child custody or abuse situations), the assay should include these metabolites.

Table 4. Treatment of Patient With Sympathomimetic Intoxication

General management
Establish intravenous access, oxygen therapy, and cardiac monitoring
Gastric decontamination
Syrup of ipecac—contraindicated. Patient unstable; potential for cocaine-induced seizure activity
Gastric lavage—not efficacious (if greater than 1 hour after ingestion); low return of cocaine packets due to size of lavage tube; may rupture bags in process
Activated charcoal—may adsorb leaking cocaine in gut
Whole bowel irrigation—(polyethylene glycol [PEG] solution) 1-2 L/h; rapid, efficacious, osmotically and electrolyte safe
Management of sympathomimetic-associated chest pain and hypertension
Benzodiazepines—first-line therapy (in high doses)
Nitroglycerin—for control of ischemic cardiac pain and hypertension
Labetalol—alpha/beta blocker (The use of propranolol will leave the alpha portion unopposed, theoretically exacerbating cocaine's toxicity.) (In theory, labetalol makes sense, but clinically, much more beta blockade than alpha)
Phentolamine—alpha blocker
Nitroprusside—for refractory hypertension
Calcium channel blockers—controversial
Thrombolytic agents if acute myocardial infarction and strict electrocardiogram criteria met. (Use cautiously, because there is high risk of intracranial bleeding in severely poisoned patients.)
Management of seizures
Administer benzodiazepines, phenobarbital, phenytoin, or general anesthesia
Management of hyperthermia
Mist spray fan, strategic ice packing, cold water lavage, cool intravenous fluids; avoid excessive antipyretic use

Amphetamines

Amphetamine and methamphetamine, along with other sympathomimetic amines, are derivatives of phenylethylamine and, thus, are structurally related. Due to their structural similarity, they, along with phenylethylamine, can cross-react with the antibody and give false-positive results by immunoassay (Table 5). Some immunoassays appear to have less cross-reactivity with ephedrine and phenylpropanolamine.[38] Interference from ephedrine, pseudoephedrine, and phenylpropanolamine may be eliminated by treatment of the specimen with periodate before immunoassay screening. Periodate in a basic solution causes oxidative cleavage of compounds with an alpha-hydroxyl group. The Emit amphetamine confirmation kit (Syva Company, Div. Dade Behring, San Jose, CA) contains sodium

hydroxide and sodium periodate for this purpose, although there has been 1 report of false-negative amphetamine results owing to use of this kit.[39] One study has shown an increase in phenylethylamine produced by putrefaction in postmortem samples may also cause a false-positive amphetamine immunoassay result.[40]

Other problems associated with amphetamine and methamphetamine immunoassay testing pertain to their stereochemistry. Both have *d* and *l* isomers, with the d isomers having the most pharmacologic action. The active ingredient in the Vicks inhaler is *l*-methamphetamine (desoxyephedrine); thus, its use could cause false-positive results with immunoassays and confirmation techniques. However, the several studies using more specific monoclonal immunoassays have shown no false-positive results when the inhaler was used as directed and only a few false positive results when the inhaler was used at twice the recommended frequency.[41,42]

Some amphetamine immunoassays used for federally regulated testing have been designed to detect only amphetamine and methamphetamine. SAMHSA requires a cutoff of 1,000 ng/mL for screening and a cutoff of 500 ng/mL for the confirmation of amphetamine and methamphetamine by GC-MS. To report a positive methamphetamine result, the laboratory must detect the metabolite amphetamine at a concentration of 200 ng/mL or higher in addition to the parent compound, methamphetamine, at or above 500 ng/mL. Kraemer and Maurer[43] reviewed and compared many of the chromatographic techniques (gas chromatography, high-performance liquid chromatography, GC-MS) available for the determination of amphetamine, methamphetamine, and amphetamine-derived designer drugs. Interference from ephedrine, pseudoephedrine, and phenylpropanolamine may also be eliminated by treatment of the specimen with periodate before analysis by GC-MS for confirmation. Although the isomers of amphetamine and methamphetamine also pose problems with confirmation testing, they can be separated and identified by specialized procedures (selective derivatization or use of chiral columns), which for federally regulated testing must be requested by the medical review officer. Thus, with determination of amphetamines, the laboratory professionals should always consider the situation (clinical vs workplace testing) when choosing amphetamine immunoassays (compare cross-reactivities) and methods of confirmation.

Table 5. Common Immunoassay Interferences for Amphetamines and Cocaine Metabolites

Test	Drugs/Metabolite and Comments
Amphetamines (amphetamine and methamphetamine)	**"Designer drugs"** MDMA ("Ecstasy; Adam") MDEA ("Eve") MDA (designer drug and also a metabolite of MDMA)
	Over-the-counter medications *l*-methamphetamine (Vicks inhaler) Ephedrine Pseudoephedrine Phenylpropanolamine
	Prescription medications Appetite suppressants Phentermine Fenfluramine Diethylpropion Ulcer treatment Ranitidine
	Hallucinogen Mescaline
	Postmortem specimens Phenylethylamine
Cocaine metabolite (benzoylecgonine)	**Meconium metabolites (fetal exposure)** *m*-hydroxybenzoylecgonine *p*-hydroxybenzoylecgonine

Conclusion

Patients who arrive at the emergency department with sympathomimetic intoxication exhibit classic signs and symptoms (toxidrome) such as hypertension, tachycardia, and hyperthermia. At high levels these drugs can also produce seizures. Because other drugs can precipitate similar clinical findings, the clinician often relies on physical examination and the results from the clinical laboratory, as the patient's history is often unreliable. A qualitative urine drug screen rather than a quantitative drug determination is a more appropriate means of assessing the source of the drug intoxication, because precise drug levels do not correlate with clinical effects. However, it is important to note that most clinical laboratories are limited as to which drugs can routinely be detected. Patient treatment often depends on the type of sympathomimetic drug and the degree of intoxication.

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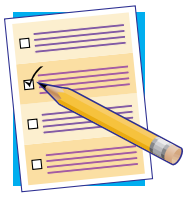

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	A	B	C	D	E
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2	☐	☐	☐	☐	☐
3	☐	☐	☐	☐	☐
4	☐	☐	☐	☐	☐
5	☐	☐	☐	☐	☐
6	☐	☐	☐	☐	☐
7	☐	☐	☐	☐	☐
8	☐	☐	☐	☐	☐
9	☐	☐	☐	☐	☐
10	☐	☐	☐	☐	☐

Multiple-Choice Questions

1. Common signs and symptoms associated with opioid intoxication include
A. miosis.
B. rhabdomyolysis.
C. hyperthermia.
D. tachycardia.
E. diaphoresis.

2. The agent of choice administered to a heroin-overdosed patient to reverse the effects of central depression is
A. niacin.
B. glucose.
C. naloxone.
D. meperidine.
E. morphine.

3. The agent used to treat heroin addiction is
A. morphine.
B. methadone.
C. meperidine.
D. fentanyl.
E. codeine.

4. Many of the hallucinogenic signs and symptoms noted with LSD ingestion may be related to its effects on receptors for
A. adrenaline.
B. noradrenaline.
C. epinephrine.
D. dopamine.
E. serotonin.

5. A common clinical finding observed with the use of marijuana is
A. miosis.
B. bradycardia.
C. flashbacks.
D. urinary retention.
E. cool dry skin.

6. The primary marijuana metabolite detected in urine by immunoassay is
A. tetrahydrocannabinol.
B. 11-hydroxy delta-9-tetrahydrocannabinol.
C. delta-9-tetrahydrocannabinol carboxylic acid.
D. delta-9-tetrahydrocannabinol.
E. cannabinol.

7. A common sign or symptom associated with high-dose cocaine use is
A. hypotension.
B. hypothermia.
C. tachycardia.
D. miosis.
E. dry skin.

8. The specimen of choice for detection of cocaine in neonates is
A. blood.
B. cerebrospinal fluid.
C. amniotic fluid.
D. urine.
E. meconium.

9. Which of the following compounds can produce a false-positive urine drug screen for amphetamines?
A. Mescaline
B. Phencyclidine
C. Caffeine
D. Phenylpropanolamine
E. Theophylline

10. Often used in the management of a sympathomimetic drug overdose for both hypertension and seizure control is (are)
A. propranolol.
B. benzodiazepines.
C. phenytoin.
D. activated charcoal.
E. polyethylene glycol.

7616