TOXICOLOGY NOTES

3 Cocaine and Sympathomemitics

Done By:
Noor AlZahrani

جامعة الملك سعود
King Saud University

COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

- Not Given!

Introduction:

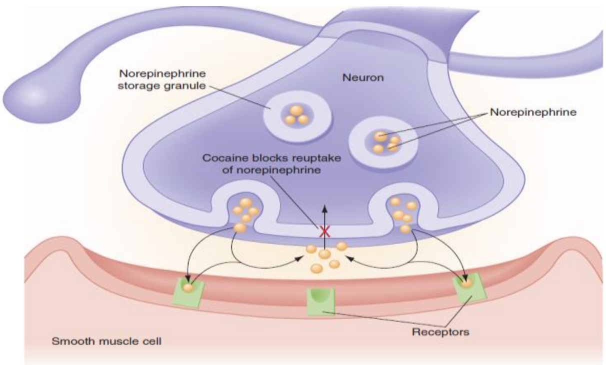
What are they?

- Cocaine, amphetamines, and derivatives of amphetamines are called *sympathomimetics*.
- These agents cause central nervous system (CNS) stimulation and a cascade of physiologic effects.

1. Pathophysiology:

Acute cocaine use causes release of **dopamine, epinephrine, norepinephrine, and serotonin**. Most important effects are adrenergic stimulation by norepinephrine and epinephrine.

- Norepinephrine causes vasoconstriction by stimulating **alpha-adrenergic** receptors on vascular smooth muscle.
- Epinephrine increases myocardial contractility and heart rate through stimulation of **beta1-adrenergic** receptors.
- In addition to causing 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. The only sympathomimetic that causes inhibition of the reuptake is Cocaine!
- 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).
- Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmic agents (as procainamide and quinidine), is responsible for the occasional conduction abnormality with acute cocaine toxicity.
- Cocaine metabolism occurs in the **liver and the plasma.**



- In the liver, primarily to the active metabolite norcocaine, which potentiates the parent drug. In the plasma, to ecgonine methyl ester via pseudocholinesterase (plasma cholinesterase). *If psedocholinesterase is dificient, cocaine intake will cause sudden cardiac arrest.*
- Ecgonine methyl ester may be protective because it is a vasodilator
- Benzoyl ecgonine is a metabolite found in the plasma and is the metabolite identified by urine toxicology screens.
- The use of ethanol with cocaine may form coca ethylene, a metabolite that may potentiate the drug's stimulatory effects.

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	"Crack"	8 sec	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

2. Clinical Features:

- 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 intoxicated patient may present agitated, combative, and hyperthermic.
- Signs and symptoms of end-organ damage may be present, including acute hypertensive emergencies.
- 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.

Hypertension
Hyperthermia
Tachycardia
Mydriasis
Diaphoresis
Central nervous system excitation

- Patients who are “speed balling,” using IV heroin (morphine) and cocaine together in the same syringe (insufflation or IV), may be **initially sedated**, and administration of naloxone may reveal the underlying cocaine intoxication.
- Mortality is high with temperatures greater than 41.1°C.

3. How to assess the toxicity:

Initial assessment and treatment should focus on rapidly fatal complications:

- Hyperthermia
- hypertensive emergencies
- cardiac dysrhythmias.
- Seizure

Hyperthermia:

Agitation with delirium increases the risk of hyperthermia.

- *Vasoconstriction and dehydration can compromise cooling*, resulting in life-threatening hyperthermia with core temperatures exceeding 106 F (41.1 C). The patient may die within 20 mins if not treated!
- Delay in recognition result in death.
- Increased motor tone can release intramuscular (CK) with rhabdomyolysis and renal and electrolyte complications.

Hypertensive emergency:

sequelae include:

- Aortic dissection
- Pulmonary edema
- Myocardial ischemia and infarction

- Intracranial hemorrhage, strokes
- Infarction of the anterior spinal artery.

Vasospasm can compromise perfusion to various organs. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers "mole who smuggles contraband across a border" with large oral ingestions. Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.

Cardiac Dyrhythmisa:

- May not be noted until cardiac output abruptly diminishes, and the patient suddenly loses consciousness.
- Sinus tachycardia is most common
- Atrial fibrillation and other supraventricular tachycardia
- Torsades de pointes or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms.
- Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Other complications:

- People who binge with continuous use causes catecholamine depletion, dehydration, 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.
- "crack dancing," a transient choreoathetoid movement disorder
- DVT is reported with cocaine use, probably secondary to effects on coagulation.
- oropharyngeal burns from the high temperature required to volatilize the drug.

- Pneumothorax, pneumopericardium, and pneumomediastinum occur from inhalational barotrauma.
- Intranasalcocaine use is associated with sinusitis and naso palatine necrosis or perforation.
- Transdermal injection of cocaine, or “skin popping,” has similar types of complications.
- Intravenous users have a high risk of infection with blood-borne viruses, local abscesses, and systemic bacterial infections, including botulism, and endocarditis.

4. Diagnostic strategies:

- Urine drug screening is unlikely to change treatment because it measures a cocaine metabolite (benzoyl ecgonine) that is typically present for 3 days (may reach 10 days) after last use. It is not very helpful in diagnosis, more important in screening if it has been used before or not!
- Cyclic antidepressants and cocaine share class Ia antidysrhythmic effects.
- Accurate diagnosis of chest pain is problematic. ST segment elevation is confounded by the presence of early repolarization.
- Serial ECGs may be helpful.
- Creatine kinase (CK)
- serum CK-MB fraction, troponin I, and troponin T are more specific in patients with atherogenic coronary disease.
- Severe, persistent headache despite normalization of blood pressure may occur with a SAH and warrants head CT and, if the scan is negative, lumbar puncture.
- Urinalysis should be checked for myoglobin, which indicates rhabdomyolysis. >> caused by aggressive muscle contraction and hyperthermia

*Urine drug screening may be beneficial in

(1) To document possible abuse

(2) To confirm cocaine as the unknown substance in body packers

(3) To differentiate paranoia from drug-induced or psychiatric causes.

*ECG

1. Sinus tachycardia ,wide complex tachycardia
2. ECG screens for dysrhythmias and conduction abnormalities from ischemia, hyperkalemia, or, more precipitously, QRS

5. 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/viral meningitis/encephalitis
- Toxicologic causes
  - Sympathomimetic/stimulants
    - Cocaine
    - Amphetamines and derivatives
    - Caffeine
    - Phencyclidine/ketamine
  - Anticholinergics
  - Serotonin syndrome
  - Sedative-hypnotic withdrawal
- Heatstroke
- Postictal state

CNS, central nervous system.

6. Differential diagnosis of Agitated delirium:

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

7. Management:

After initial airway assessment:

- Physical restraints to obtain complete vital signs and to secure IV access.
- Empirical therapy with **IV dextrose and thiamine or assessment with a bedside blood glucose monitor.**
- **IV benzodiazepines may be necessary** "usually given in huge doses and may cause respiratory depression so intubate immediately because the antidote will kill the patient. This is also may happen in case of seizure"

Pharmacological sedation:

- In adults, IV diazepam can be administered in increments of 10 mg every 5 minutes until sedation is achieved.
- In wildly agitated patients in whom 20 to 30 mg of diazepam has no notable effect, the increments may be increased carefully by 20 mg each subsequent dose with close monitoring.

Hyperthermia:

- rapid cooling.
- Patients who sustain elevated core temperatures greater than (41 C) for more than 20 minutes are likely to stabilize transiently, then develop fatal multisystem organ failure, often heralded by DIC.
- Patients should have continuous monitoring of core temperature with a rectal probe.
- It is crucial to reduce core temperature to (38.8? C) within 20 minutes.
- Cooling blankets are insufficient. Ice water, wet sheets with large fans, and packing the entire body in ice with continuous monitoring of core temperature can be used.
- These patients often require aggressive fluid resuscitation.

Hypertensive Emergwncies

- Benzodiazepines restore the CNS inhibitory tone on the peripheral nervous system.
- With evidence of end-organ damage, IV nitroglycerin or nitroprusside can be used.
- Phentolamine, a direct alpha-adrenergic antagonist, is the antihypertensive of choice.
- It can be titrated slowly using repeat IV doses of 1 to 5 mg with blood pressure monitoring.
- Beta Blockers may cause paradoxical hypertension with cocaine.
- Beta Blockers use in cocaine-related chest pain syndromes should be avoided.

Dysrhythmia:

- atrial or ventricular.
- Atrial fibrillation and supraventricular tachycardias are likely due to sympathetic stimulation and often respond to benzodiazepines. Beta-adrenergic antagonists should be avoided. Even Labetalol which has mild alpha function.
- When the cause of a wide-complex tachycardia from cocaine is unknown, an empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus
- treats sodium channel blockade and potential cardiotoxicity from hyperkalemia.

A-Lidocaine

- may increase seizure risk and mortality and is therefore reserved for patients with ventricular dysrhythmias for whom bicarbonate therapy has failed and who have already received benzodiazepines
- most useful for ventricular dysrhythmias with cocaine-associated MI.

B-Amiodarone: is not well studied, but may be beneficial for ventricular dysrhythmias.

8. Cocaine-related chest pain:

- Chest radiograph to identify:- **aspirated foreign bodies, pneumothorax or pneumomediastinum from inhalational barotraumas, Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction, or endocarditis with septic pulmonary emboli in IV drug abuse.**

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

- Cocaine induces coronary vasoconstriction and increase myocardial oxygen demand.
- Platelet aggregation is enhanced through prothrombogenic and antifibrinolytic pathways.
- Patients with positive serum enzymes for MI have significant angiographic stenosis
- 18% still have significant disease by angiogram.
- Other predictors of significant disease in this group included elevated cholesterol and prior diagnosis of coronary disease or MI.
- Patients with a history of coronary stent placement are at a high risk of thrombosis with cocaine use
- benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early.
- Aspirin and nitrates also should be administered. In patients meeting ECG criteria for MI with persistent chest pain and hypertension and a clear history of acute cocaine intoxication,
- coronary vasodilation with IV phentolamine (1 mg) given slowly should be considered.
- Morphine sulfate also can be used to treat pain.

- Patients with persistent chest pain and ST segments strongly suggestive of MI can be considered for percutaneous intervention in the catheterization laboratory or thrombolytic therapy, assuming there are no contraindications such as uncontrolled severe hypertension.
- beta-adrenergic antagonists, including labetalol, are contraindicated during acute cocaine toxicity
- Patients with cocaine-related chest pain without other risk factors who have normal ECGs and cardiac enzymes are at low risk for myocardial infarction.

9. 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.
- Body packers are likely to know the exact number of packets they ingested.
- A body packer may present without symptoms to the ED.
- The body packer should be placed immediately on continuous cardiac monitoring, with large-bore IV access.
- An abdominal radiograph may confirm foreign bodies
- When uncertainty persists, a contrast study is warranted.
- When evidence of cocaine toxicity is manifest, 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.
- CT and contrast abdominal radiographs may fail to detect isolated packets that contain potentially fatal quantities of cocaine.
- Endoscopic retrieval is discouraged because of concern over packet rupture during the procedure.

Body Stuffers

- A "body stuffer" is an individual who attempts to conceal evidence of cocaine possession by swallowing the drug while pursued by law enforcement officials.
- These are usually unplanned events with generally small quantities of drug intended for personal use.

10.Disposition:

- can be discharged after the acute intoxication resolves. These patients may be extremely sleepy from catecholamine depletion, and it is best to discharge them with a responsible adult.
- Patients who develop complications should be
- admitted to the intensive care unit for further treatment.

Persistent chest pain
Electrocardiogram 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.

- Patients with chest pain who are acutely intoxicated and who show dynamic changes on the ECG, dysrhythmias, or congestive heart failure or patients requiring vasodilators or reperfusion should be admitted.
- These patients require further evaluation of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use.
- After a 12-hour monitored observation period, patients with a benign clinical course and negative serum enzyme markers can be discharged.
- 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 negative contrast radiographic study.

11.Amphetamin:

- Enhance release of catecholamines from presynaptic nerve terminals
- Usually taken as pills, but occasionally are crushed and injected.
- CNS stimulation results in nearly identical sympathomimetic effects to those from cocaine, but not with the same frequency or intensity.

Patients are at risk for:-

- Hyperthermia
- hypertensive emergencies
- Dysrhythmias
- myocardial ischemia
- hyperkalemia associated with rhabdomyolysis.
- 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 treating an intoxicated patient.
- The management follows the same guidelines as for cocaine, although the duration of toxicity tends to be longer for amphetamines.

12. 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."
- life-threatening hyponatremia
- may alter release of endogenous stores of vasopressin.
- urine samples with a relatively high urine sodium level, similar to SAIDH.
- Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction.
- 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.
- In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotoninergic neurons.

13. Metamphetamine:

- 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.

KEY CONCEPTS

- Rapid sedation with an IV 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 generally contraindicated.
- Wide-complex rhythms secondary to cocaine may respond to IV bicarbonate therapy.
- Cocaine body packers who become symptomatic need immediate surgery.
- Amphetamine symptoms and effects last longer than those produced by cocaine.

Questions

1) Which one of the following is not a cocaine toxicity feature?
   a. Palpitation
   b. Fever
   c. Headache
   d. Dry skin

2) Arrhythmia caused by cocaine can be treated by ?
   a. Na-bicarb
   b. Labetalol
   c. Carvidilol
   d. Atenelol

Answers:

1st Questions: d	2nd Questions: a	: