Clinical toxicology

CNS stimulants

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Introduction

Amphetamines

widely abused for their

- stimulant
- euphoriant effects
- anorexiant properties, and
- as dance drugs

The medical indications for amphetamine are limited

- treatment of narcolepsy
- hyperactivity in children, and
- appetite suppression in obesity

Dextroamphetamine methamphetamine and methylphenidate

The drugs is sold as a powder or tablet

- inhaled or snorted
- Orally
- smoked
- injected intravenously.

Pharmacology of amphetamine

- direct α-adrenergic stimulants
- inhibit neurotransmitter reuptake
- increase release from store of neurotransmitters norepinephrine, serotonin, and dopamine

These effects both centrally and on periphry

- ✓ leading to stimulation of the cerebral cortex, medullary respiratory center, and reticular activating center.

Table 76-1 -- Clinical Presentation of Acute Amphetamine Toxicity

Severity	Signs and Symptoms
Mild	Nausea, vomiting, abdominal pain, widely dilated pupils, flushing or pallor, sweating, headache, restlessness, tremor, hyperreflexia, irritability, pallor, bruxism (grinding of teeth), trismus (jaw clenching), palpitations
Moderate	Hyperactivity, confusion, aggression, muscle rigidity, tachycardia, tachypnea, hypertension, chest discomfort, mild pyrexia, hallucinations, dehydration.
Severe	Delirium, hyperpyrexia (>40°C), hypertension or hypotension, seizures, coma, renal failure associated with rhabdomyolysis, cardiac dysrhythmias (atrial and ventricular tachydysrhythmias)
Potentially fatal	Ventricular fibrillation, myocardial infarction, cerebrovascular accident (usually cerebral hemorrhage), extreme hyperthermia (may precipitate DIC), acute cardiac failure, repeated seizures, cerebral edema with brainstem compression secondary to hypoxia or hyponatremia
Withdrawal	Apathy, depression, lethargy, anxiety, sleep disturbances, myalgia, abdominal pain, increased appetite
Chronic toxicity	Paranoid psychosis with visual, tactile, or olfactory hallucinations; cardiomyopathy, vasculitis, possible serotoninergic hemotoxicity

LABORATORY STUDIES

1-Arterial Blood Gas Analysis

The most common finding is a respiratory alkalosis due to tachypnea secondary to respiratory center stimulation

2-Electrolytes, BUN, and Creatinine

The sympathomimetic effects of amphetamines may lead to hypokalemia

Hypernatremia may result from dehydration.

Hyperglycemia may result from excessive sympathetic stimulation

3-Toxicology Screens.

Blood and urine tests for amphetamines may confirm amphetamine intoxication and possibly exclude other causes

Treatements

- Stabilization
- GI decontamination(Syrup of ipecac should be avoided)
- Orogastric lavage if 1-2 hour since ingestion activated charcoal 50g adult,1g/kg in child

- cardiac dysrhythmias (benzodiazepines, esmolol, lidocaine, Ca-channel blocker

- seizure (Lorazepam, barbiturate, midazolam)
- Hyperthermia(I.V.fluid, rapid cooling
- agitation and psychosis (diazepam, haloperidol).

Caffeine

- Many people depend on stimulants to keep them alert and improve their productivity
- persons consuming an average of 200 mg of caffeine per day, It is found in chocolate, carbonated sodas, and coffee as well as in over-the-counter oral analgesics, migraine treatments, and products promoting alertness

Category	Product	Amount of Caffeine
Coffee	Brewed coffee	40-180 mg/5 oz
Tea	Brewed commercial tea	20-90 mg/5 oz
Soft drinks	Coca Cola	46 mg/12 oz
Food	Milk chocolate	2-7 mg/8 oz
Medications	Cafergot	100 mg/tablet
	Excedrin	65 mg/tablet
	Panadol extra	65 mg/tablet

Pharmacology of caffeine

(1) adenosine receptor ***antagonism***,
(2) phosphodiesterase ***inhibition***, and
(3)***enhanced*** intracellular calcium levels.

- vasoconstriction, hypertension, tremor, and agitation
- inhibits phosphodiesterases, causing increased levels of cyclic AMP, which results in increased levels of catecholamines
- Muscle contractility is enhanced through increased intracellular calcium levels and increased permeability of the sarcoplasmic reticulum to calcium.
- Stimulation of gastric acid and intestinal secretions and lowering of lower esophageal sphincter tone by caffeine commonly result in diarrhea and abdominal cramping

In adults, ingestion of 500–1000 mg of caffeine show the following acute toxic effect

Table 36-4 -- Clinical Effects of Caffeine Toxicity

Mild and Common	Severe and Uncommon
Sinus tachycardia	Seizure
Reflex bradycardia with phenylpropanolamine	Hypertensive crisis
Hypertension	Hyperthermia
Nausea, vomiting, diarrhea, cramps	Myocardial infarction/chest pain
CNS agitation, anxiety	Delirium
Palpitations	Intracerebral hemorrhage

Treatment in caffeine toxicity

Effect	Therapy	Dose (Adult)
Decontamination	Activated charcoal	50–100 g PO
Dysrhythmia	Benzodiazepines	Diazepam: 5–10 mg IV q 5–10 min
		Lorazepam: 1–2 mg IV q 5 min
	Esmolol	Esmolol: LD 500 µg/kg IV over 1 min; follow with 50 µg/kg/min IV infusion; titrate up q 5 min to a max of 200 µg/kg/min prn
	Lidocaine	Lidocaine: 1–1.5 mg/kg IV bolus over 2–3 min; may repeat dose of 0.5 mg/kg in 5–10 min up to a total of 3 mg/kg
	Procainamide	Procainamide: LD 15–18 mg/kg given as slow infusion over 25–30 min; maintenance dose 1–6 mg/min by continuous IV infusion

Hypertension	Benzodiazepines	Diazepam: 5–10 mg IV q 5–10 min
		Lorazepam: 1–2 mg IV q 5 min
	Sodium nitroprusside	Sodium nitroprusside: 0.5 µg/kg/min, increase by 0.5 µg q 5 min until desired effect; maximum dose of 10 µg/kg/min
Seizures	Benzodiazepines	Diazepam: 5–10 mg IV q 5–10 min
		Lorazepam: 1–2 mg IV q 5 min
	Phenobarbital	Phenobarbital: 10–20 mg/kg IV given at a rate of 25–50 mg/min

Nausea/vomiting	Rehydration if necessary	Titrate crystalloids to maintain urine output of 1–2 mL/kg/hr
	Potassium/electrolyte replacement	Replace electrolytes as needed.
	Antiemetics	
	Metoclopromide	Metoclopromide: *Adult*= 5–10 mg IV, PO, or IM up to a maximum dose of 1 mg/kg
		Pediatric: 0.1 mg/kg to maximum 10 mg dose
	Ondansetron	Ondansetron
		Adult: 0.15 mg/kg IV (maximum 8 mg dose)
		Pediatric: ≤40 kg 0.15 mg/kg/IV
		>40 kg 4 mg IV

Theophylline

- Theophylline inhibits(PDEs) preventing hydrolysis of cyclic AMP and cyclic GMP
- competitive antagonist at adenosine receptors

- therapeutic serum concentrations (5–15 mg/L)
- Seizure & cardiac arrhythmias at 28–70 mg/L

- induced tachycardia, hypokalemia , lactic acidosis, and hyperglycemia.

❖ nausea and vomiting may result from

- direct central nervous system (CNS) stimulation of the chemoreceptor trigger zone
- relaxation of lower esophageal sphincter tone
- phosphodiesterase inhibition, and
- increases in gastric acid secretion

❖Adenosine receptor antagonism in the brain has been implicated in the seizures and status epilepticus associated with severe theophylline poisoning.

Clinical Presentation of Theophylline Toxicity

Nausea, repeated vomiting
Tachycardia, tachypnea, wide pulse pressure
Restlessness, tremors, seizures, status epilepticus
Anion gap metabolic acidosis, respiratory alkalosis
Electrolytes: hypokalemia, low bicarbonate, hyperglycemia
Leukocytosis
Electrocardiogram: sinus tachycardia, supraventricular tachycardia, multifocal atrial tachycardia in chronic obstructive pulmonary disease, ventricular dysrhythmias

treatments

- Seizures should be treated aggressively with benzodiazepines and, if required, barbiturates,
- Treatment of life-threatening supraventricular dysrhythmias includes the correction of hypoxia and any fluid and electrolyte abnormalities, cardioversion, and diltiazem if needed.
- Adenosine may not be effective in this setting, with larger doses required to overcome theophylline's adenosine receptor antagonism.
- Ventricular dysrhythmias may be treated with lidocaine, cardioversion, or defibrillation as needed.
- Hypotension treated with an adequate crystalloid fluid followed by peripheral α-adrenergic receptor agonists, such as norepinephrine

Cocaine

- High lipid solubility
- Very Good absorption (nasal, oral, rectal, inhalation)
- Oral peak 60minutes
- Nasal insufflations peak 30minutes

Pharmacology of cocaine

- inhibits the reuptake of both epinephrine and norepinephrine and stimulates the presynaptic release of norepinephrine (periphery)
- Enhanced release of norepinephrine and excitatory amino acids and/or blockade of neuronal reuptake of dopamine, serotonin, and excitatory amino acids (centrally)
- **Na-channel blockade**

The effects of cocaine are related to

- sympathetic nervous system effects
- central nervous system stimulation, and
- local anesthetic effects

- The initial effect of cocaine on the cardiovascular system is vagotonic, producing a transient bradycardia; however, the increased sympathetic stimulation rapidly produces tachycardia and hypertension

Table 75-1 -- Clinical Presentation of Cocaine Toxicity

Signs and Symptoms	Physical Findings *	Laboratory and Imaging Abnormalities ‡
Chest pain	Sympathomimetic toxidrome	Electrolyte imbalance (lactic acidosis, hyperglycemia, hypokalemia, hyperkalemia, renal failure)
Shortness of breath	Altered mental status	Chest radiography (pneumothorax, pneumomediastinum, pneumonia, pulmonary infarction)
Anxiety	Hyperthermia (rectal temp)	Electrocardiography (dysrhythmias, ST-T wave changes, conduction blocks)
Palpitations	Hypertension	Arterial blood gas (hypoxia, respiratory alkalosis, metabolic acidosis)
Dizziness	Tachycardia	Head CT (subarachnoid, intracranial hemorrhage, bland infarcts)
Headache	Mydriasis	Lumbar puncture (subarachnoid bleed)
Nausea	Tachypnea	Creatine phosphokinase (rhabdomyolysis)
Vomiting	Diaphoresis	CK-MB isoenzymes (myocardial infarction)
Hallucinations	Hyperactive bowel sounds	Troponin I (myocardial infarction)
Psychosis	Epistaxis, nasal perforation	Urine toxicology screen
Confusion	“Track marks”	
Fevers	Other findings specific to presenting complaints (such as rales for congestive heart failure)	
Seizures		
Suicidal or homicidal ideation		
Spontaneous abortion		

Treatment

- Agitation
  sedation with benzodiazepines

- Hyperthermia
  cooled with restricted activity; iced water baths

- Supraventricular tachycardia
  benzodiazepines followed by calcium-channel antagonists

- Myocardial Ischemia
  with benzodiazepines, aspirin, and sublingual nitroglycerin

- Seizures

Benzodiazepines If high doses do not control the seizures, phenobarbital should be used

Nicotine

- it is second only to caffeine as the most widely used CNS stimulant and second only to alcohol as the most abused drug.

- In low doses, nicotine causes ganglionic stimulation by depolarization. At high doses, nicotine causes ganglionic blockade

Clinical presentation

- Gastrointestinal symptoms develop soon after the ingestion of nicotine-containing products and include an oral burning sensation, increased salivation, nausea, and vomiting.
- Headache, agitation, dizziness, confusion, and lethargy may develop after moderate nicotine exposure, Seizures and coma may develop early after the ingestion of large amounts of nicotine.
- tachypnea followed by bradypnea or apnea, dyspnea, increased bronchial secretions, and cyanosis
- Initial, transient tachycardia and hypertension due to catecholamine release may be quickly followed by bradycardia and hypotension

LABORATORY STUDIES

- Nicotine and its major metabolite, cotinine, are easily detected in the urine of persons with active or passive exposure to cigarette smoke.

- Nicotine is readily detected and can be quantified in plasma or serum soon after the exposure

Treatment of Nicotine Poisoning

- Stabilization/monitoring
- Gastric decontamination with oral activated charcoal
- Seizures

Diazepam 5-10 mg/kg i.v. for adult and 0.1mg/kg in pediatric

- Pulmonary edema or excess secretions

Atropine 0.02 mg/kg IV (pediatric), repeat as necessary, 2-3 mg IV (adult), repeat as necessary

- Hypotension(Fluid resuscitation)

- Acidification of the urine should enhance the elimination of nicotine via ion-trapping but is not used because it can aggravate metabolic acidosis