Clinical Toxicology
Toxicity of CNS Stimulants
5th Year
(Lab 4)

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Introduction:

- CNS stimulants represent a diverse group of chemically & pharmacological dissimilar compounds.

- There are many CNS stimulants including: amphetamine, theophyline, caffeine, cocaine, strychnine, & camphore .

- They may cause acute or chronic toxicity due to drug abuse.

Amphetamine:

- Toxicity of Amphetamines (amphetamine & amphetamine-like drugs) may results from:

- Prescribed medications: combination of dextroamphetamine & amphetamine (brand name: Adderall) & dextroamphetamine (brand name: Dexedrine) are approved for the treatment of attention deficit hyperactivity disorder (ADHD) & also for narcolepsy (a neurological condition marked by severe daytime drowsiness).

- Street drug abuse: recreational "street" amphetamine, is another cause of toxicity.

Mechanism of toxicity:

- Amphetamine induces CNS stimulation, mainly by causing release of catecholamines into central synaptic spaces & inhibiting their reuptake into nerve endings.

- Both CNS and PNS are stimulated due to sympathomimatic effects of catecholamines.

- A problem that frequently encountered by amphetamine users is tolerance to the anorexiant & euphoric actions.

- Because of tolerance to the anorexiant & euphoric actions, users may need to increase the dose, sometimes approaching several hundred milligrams daily.

- Toxic psychosis may appear after months of continued use.

Characteristics of poisoning:

- Clinical manifestations of acute & chronic amphetamine toxicity are listed in Table 1.

- The clinical effects of amphetamines are largely related to the stimulation of central & peripheral adrenergic receptors.

- Compared to cocaine, amphetamines are less likely to cause seizures, dysrhythmias, & myocardial ischemia.

- Tachycardia & hypertension are the most common manifestations of cardiovascular toxicity.
- Visual & tactile hallucinations, as well as psychoses, are common.
- Other sympathetic findings include mydriasis, diaphoresis, & hyperthermia.
- Rhabdomyolysis from amphetamine toxicity usually results from agitation & hyperthermia.
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- Direct CNS effects may result in seizures.
- Euphoria may account for the widespread abuse potential of amphetamine.
- Death from amphetamine toxicity most commonly results from hyperthermia, dysrhythmias, & intracerebral hemorrhage.
- The lethal dose of amphetamine varies. The acute lethal dose in adults has been reported at 20 to 25 mg/kg. Death from as little as 1.5 mg/kg in adult has also been noted.

Table 1. Clinical manifestations of acute & chronic amphetamine toxicity

Clinical Manifestations of Amphetamine Toxicity	
Acute	Mydriasis
Cardiovascular system	Tremor
Hypertension	Nausea
Tachycardia	**Other organ system manifestations**
Dysrhythmias	Rhabdomyolysis
Myocardial ischemia	Muscle rigidity
Aortic dissection	Acute lung injury
Vasospasm	Ischemic colitis
Central nervous system	**Laboratory abnormalities**
Hyperthermia	Leukocytosis
Agitation	Hyperglycemia
Seizures	Hyponatremia
Intracerebral hemorrhage	Elevated CPK
Headache	Elevated liver enzymes
Euphoria	Myoglobinuri
Anorexia	
Bruxism	**Chronic**
Choreoathetoid movements	Vasculitis
Hyperreflexia	Cardiomyopathy
Paranoid psychosis	Pulmonary hypertension
Other sympathetic symptoms	Aortic and mitral regurgitation
Diaphoresis	Permanent damage to dopaminergic
Tachypnea	and serotonergic neurons

Management:

- Table 2. summarizes the therapeutic approach to a patient with amphetamine toxicity.

- Hyperthermia requires immediate interventions to achieve cooling.

- Because agitation & resistance against physical restraint may lead to rhabdomyolysis & continued heat generation, intravenous chemical sedation should be instituted immediately.

- The most appropriate choice of sedation is benzodiazepines because they have a high therapeutic index & good anticonvulsant activity.

- Antipsychotics, particularly potent dopamine antagonists such as haloperidol & droperidol, are frequently recommended by others for amphetamine-induced delirium.

- Antipsychotics may lower the seizure threshold, may cause acute dystonia & cardiac dysrhythmias.

- Patients with acute renal failure, acidemia, & hyperkalemia will likely require urgent hemodialysis.

Table 2. Management of patients with amphetamine toxicity

Management of Patients with Amphetamine Toxicity
Agitation
Benzodiazepines (usually adequate for the cardiovascular manifestations)
Diazepam 10 mg (or equivalent) IV, repeat rapidly until the patient is calm (cumulative dose may be as high as 100 mg of diazepam)
Seizures
Benzodiazepines
Barbiturates
Propofol
Hyperthermia
External cooling
Control agitation rapidly
Gastric decontamination and elimination
Activated charcoal for recent oral ingestions
Hypertension
Control agitation first
α-Adrenergic receptor antagonist (phentolamine)
Vasodilator (nitroprusside, nitroglycerin or possibly nicardipine)
Delirium or hallucinations with abnormal vital signs
If agitated: benzodiazepines
Delirium or hallucinations with normal vital signs
Consider risk/benefit of haloperidol or droperidol

THANK YOU FOR YOUR ATTENTION