Al-Mustaqbal University College
Department of Pharmacy
5th stage
Clinical Toxicology
Lecture: 3

Hypoglycemic drugs & CNS Stimulants Toxicity

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Oral Hypoglycemic Drugs Toxicity

Sulfonylurea compounds are among the most widely prescribed medications in the world to treat patients with type II diabetes.

First-generation sulfonylureas (chlorpropamide and tolbutamide) have longer half-lives.

Second-generation sulfonylureas were introduced in 1984 (as glipizide and glimepiride) are more potent and have shorter half-lives than the first-generation sulfonylureas.

Oral Hypoglycemic Drugs Toxicity

Other agents besides sulfonylureas are used to treat type II diabetes, including

- ✓**Biguanides (Metformin, Phenformin and Buformin)**
- ✓**Alpha-glucosidase inhibitors (Acarbose and Miglitol)**
- ✓**Thiazolidinediones (Pioglitazone and Rosiglitazone)**

These drugs even in excessive dosage, these agents do not induce hypoglycemia.

Oral Hypoglycemic Drugs Toxicity

Sulfonylureas MOA :

These drugs are mainly effective in patients with functional pancreatic beta cells.

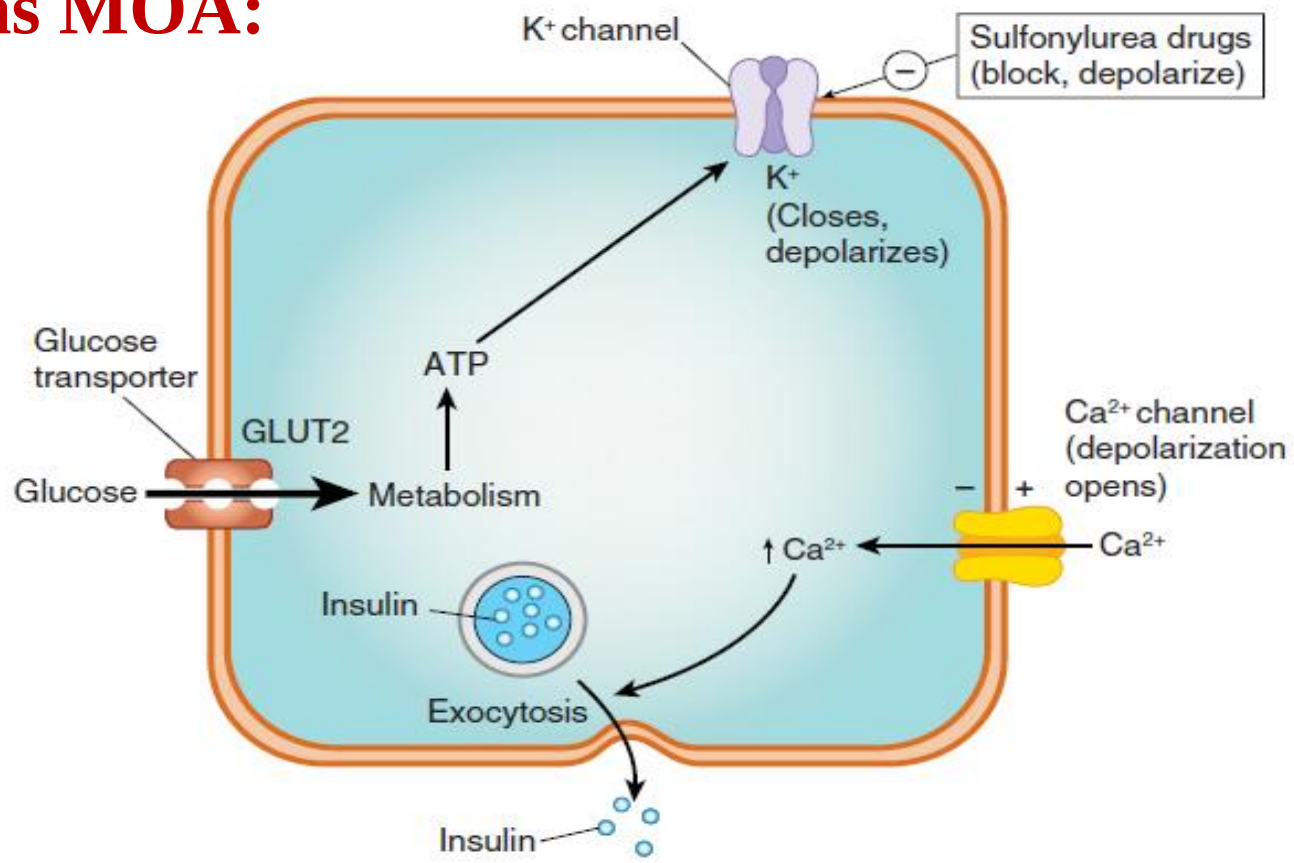
Sulfonylureas bind to receptors that are associated with potassium channels sensitive to ATP in beta-cell membrane.

The binding inhibits efflux of potassium ions from the cells, resulting in depolarization, influx of calcium ions, and release of preformed insulin.

Sulfonylureas may also cause the decrease of serum glucagon and potentiate the action of insulin at the extrapancreatic tissues.

Oral Hypoglycemic Drugs Toxicity

Sulfonylureas MOA:



Oral Hypoglycemic Drugs Toxicity

Sulfonylureas pathophysiology:

Patient presentation depends on the severity and duration of hypoglycemia.

Signs may include the following:

- ✓ **Altered mental status, Generalized weakness, Diaphoresis (sever sweating)**
- ✓ **Tachycardia, Tachypnea, Transient neurologic deficit**
- ✓ **Pallor, Seizure, Cyanosis, Coma, Hypothermia**

Oral Hypoglycemic Drugs Toxicity

Laboratory Studies:

Tests for oral hypoglycemic agent exposure may include the following:

1. **Fingerstick and/or serum glucose test to detect hypoglycemia (If hypoglycemia does not occur within the first 2-4 hours after suspected ingestion, then other laboratory tests are unnecessary.)**
2. **Baseline CBC count (in symptomatic patients)**
3. **Baseline electrolytes, especially potassium (in symptomatic patients)**
4. **Imaging Studies:**
5. **Head CT scanning is recommended in patients with an altered mental status, a focal neurologic defect, or new-onset seizures.**

Oral Hypoglycemic Drugs Toxicity

Treatment:

- ✓ **The main goal in oral hypoglycemic agent exposure is supportive care, which includes airway, breathing, and circulation.**
- ✓ **Ipecac is not recommended because of the possibility of aspiration in patients with a depressed mental status.**
- ✓ **Administer activated charcoal as soon as possible, preferably within 1 hour of ingestion.**
- ✓ **Hemodialysis is not indicated because most sulfonylureas have high protein binding.**

Oral Hypoglycemic Drugs Toxicity

Treatment:

- ✓ **Intravenous administration of glucose rapidly resolves the effects of hypoglycemia.**
- ✓ **Its onset is quicker than oral administration of sugar.**
- ✓ **It is safer in patients with a depressed mental status who should not take anything by mouth for fear of aspiration.**

Oral Hypoglycemic Drugs Toxicity

Treatment:

✓**Glucagon** is helpful and can be administered:

1. **Intravenously**
2. **Intramuscularly**
3. **Subcutaneously.**

✓**Glucagon is particularly useful in the intramuscular mode when intravenous access cannot be obtained immediately.**

Oral Hypoglycemic Drugs Toxicity

Treatment:

- ✓ **If a patient is lethargic, then oxygen and continuous cardiac monitoring are indicated.**
- ✓ **Until the patient totally regains mental status, do not administer anything by mouth.**

CNS Stimulants

Stimulants are substances that induce a number of characteristic symptoms.

CNS effects include alertness with increased vigilance, a sense of well-being, and euphoria.

Many users experience insomnia and anorexia, and some may develop psychotic symptoms.

CNS Stimulants

Stimulants have peripheral cardiovascular activity, including increased blood pressure and heart rate.

They include a broad category of substances, including those prescribed for medical conditions; those manufactured for illegal substance abuse; and those found in over-the-counter (OTC) decongestants, herbal extracts, caffeinated beverages, and cigarettes.

CNS Stimulants - Amphetamine

Amphetamines

Amphetamines are a class of compounds increasingly abused in wide regions of the world.

The phenylethylamine structure of amphetamines is similar to catecholamine, dopamine, and serotonin agonists (biogenic amines) which may explain their actions.

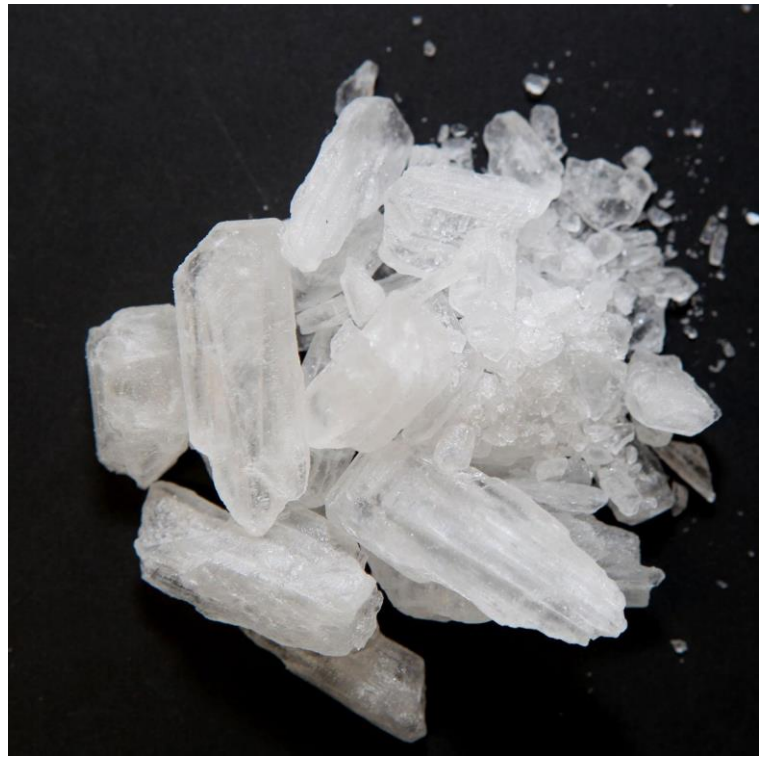
The routes of amphetamine administration may be oral (ingestion), inhalation (smoke), or injection (intravenous).

Oral use is associated with an approximate 1-hour lag time before onset of symptoms.

CNS Stimulants - Amphetamine

Amphetamines Pathophysiology:

Amphetamines are a group of structurally related compounds that produce central nervous system (CNS) and peripheral nervous system (PNS) stimulation.



CNS Stimulants - Amphetamine

Central nervous system effects

Amphetamine compounds cause a general efflux of biogenic amines from neuronal synaptic terminals (indirect sympathomimetics).

They inhibit specific transporters responsible for reuptake of biogenic amines from the synaptic nerve ending and presynaptic vesicles.

Amphetamines also inhibit monoamine oxidase, which degrades biogenic amine neurotransmitters intracellularly.

The net effect is an increase of neurotransmitter release into the synapse.

Elevated catecholamine levels usually lead to a state of increased arousal and decreased fatigue.

Increased dopamine levels at synapses in the CNS may be responsible for movement disorders , schizophrenia, and euphoria.

CNS Stimulants - Amphetamine

Peripheral nervous system effects

Catecholaminergic (sympathomimetic) effects of amphetamines include inotropic and chronotropic effects on the heart, which can lead to tachycardia and other dysrhythmias.

The vasoconstrictive properties of the drugs can lead to hypertension and/or coronary vasospasm.

CNS Stimulants - Amphetamine

Clinical Presentation

Physical examination findings may demonstrate the strong central nervous system and peripheral nervous system stimulation produced by amphetamine compounds.

Modification of the basic amphetamine molecule produces compounds with variable effects on target organs.

Methamphetamine produces prominent central nervous system effects with minimal cardiovascular stimulation.

Individuals who chronically use amphetamines intravenously are at risk of infection and vascular injury.

CNS Stimulants - Amphetamine

General Clinical Presentation

- ✓ **Weight loss**
- ✓ **Hyperactivity, confusion, and agitation (may combine to produce severe hyperthermia, which can be worse in physically restrained individuals)**
- ✓ **Diaphoresis**
- ✓ **Mydriasis**
- ✓ **Anorexia**

CNS Stimulants - Amphetamine

Cardiovascular Clinical Presentation

- ✓ **Alpha- and beta-adrenergic stimulation can lead to systolic and diastolic blood pressure increases.**
- ✓ **Heart rate may be unchanged or slow in response to hypertension.**
- ✓ **Increasing doses produce tachycardia and other dysrhythmias**
- ✓ **Hypertensive crisis or vasospasm may lead to stroke.**

CNS Stimulants - Amphetamine

Respiratory Clinical Presentation

- ✓**Persons who smoke amphetamines can develop respiratory distress secondary to acute lung injury.**

CNS Clinical Presentation

- ✓**Increased alertness**
- ✓**Euphoria**
- ✓**Confusion or agitation**
- ✓**Stroke caused by acute amphetamine toxicity**

CNS Stimulants - Amphetamine

Cutaneous Clinical Presentation

- ✓ Skin flushing
- ✓ Infected deep ulcerations (ecthyma)
- ✓ Skin track marks, cellulitis, abscesses, phlebitis, or vasculitis with intravenous use

Gastrointestinal Clinical Presentation

- ✓ Nausea or vomiting

Dental Clinical Presentation

- ✓ "Meth mouth," a condition of eroded teeth

CNS Stimulants - Amphetamine

Amphetamine Toxicity Treatment

- ✓Patients with amphetamine intoxication who present with **no life-threatening** signs or symptoms may be treated with **sedation and observation**.
- ✓In patients with **acute oral ingestion**, GI decontamination is performed by the administration of **activated charcoal**.
- ✓**Gastric lavage** often is **not necessary** but may be performed when the patient presents with immediately **life-threatening** intoxication **shortly after ingestion**.
- ✓**Whole-bowel irrigation** may be indicated in suspected cases of **body stuffing or body packing** (large quantities of drugs in wrapping for international transport or drug hiding, respectively).
- ✓**Foley catheter** placement may be useful to **monitor urine output**, particularly in situations in which diuretics are administered to **manage pulmonary edema**. Patients often have **decreased urination** due to the effects on bladder sphincter muscles to prevent passing urine.

CNS Stimulants-Amphetamine

Amphetamine Toxicity Treatment

- ✓**Agitation or persisting seizures** in patients with amphetamine toxicity requires generous titration of **benzodiazepines** and a calm soothing environment.
- ✓Significant cardiac dysrhythmias may require **antidysrhythmic**.
- ✓Cardiogenic pulmonary edema can be managed with **nitroglycerin** and **diuretics**.

CNS Stimulants – Cocaine

Cocaine is a powerfully addictive stimulant drug made from the leaves of the coca plant native to South America.

Although it can be use for valid medical purposes, such as local anesthesia for some surgeries, recreational cocaine use is illegal.

Cocaine looks like a fine, white, crystal powder.

CNS Stimulants – Cocaine

Signs and symptoms:

There are 3 phases of acute cocaine toxicity.

In fatal cases, the onset and progression are accelerated, with convulsions and death frequently occurring in 2-3 minutes, though sometimes in 30 minutes.

CNS Stimulants – Cocaine

Phase I (early stimulation) is as follows:

- ✓**CNS findings:** Mydriasis, headache, nausea, vomiting, vertigo, nonintentional tremor (eg, twitching of small muscles, especially facial and finger), preconvulsive movements, and pseudohallucinations.
- ✓**Circulatory findings:** Possible increase in blood pressure (BP), slowed or increased pulse rate, and pallor
- ✓**Respiratory findings:** Increase in rate and depth
- ✓**Temperature findings:** Elevated body temperature
- ✓**Behavioral findings:** Euphoria, agitation, excitation, restlessness, and emotional instability.

CNS Stimulants – Cocaine

Phase II (advanced stimulation) is as follows:

- ✓ **CNS findings:** generalized seizures, decreased responsiveness to all stimuli, and incontinence
- ✓ **Circulatory findings:** Hypertension; tachycardia; and ventricular dysrhythmias.
- ✓ **Respiratory findings:** Tachypnea, dyspnea, gasping, and irregular breathing pattern
- ✓ **Temperature**: Severe hyperthermia

CNS Stimulants – Cocaine

Phase III (depression and premorbid state) is as follows:

- ✓ **CNS:** Coma, areflexia, pupils fixed and dilated, and loss of vital support functions
- ✓ **Circulatory:** Circulatory failure and cardiac arrest
- ✓ **Respiratory:** Respiratory failure, gross pulmonary edema, cyanosis, and paralysis of respiration

CNS Stimulants – Cocaine

Management:

The general objectives of pharmacotherapeutic intervention in cocaine toxicity are to reduce the CNS and cardiovascular effects of the drug by using benzodiazepines initially.

Then to control clinically significant tachycardia and hypertension while simultaneously attempting to limit deleterious drug interactions.

Hyperthermia may be treated with convection cooling, which involves spraying the patient's body with water.

Rapid fluid resuscitation promotes urine output.

CNS Stimulants – Cocaine

Pathophysiology

Tachydysrhythmias cause most acute cocaine-related deaths.

Other causes of sudden death include stroke, hyperthermia, and the consequences of agitated delirium.

Multisystem effects of cocaine pay particular attention to the assessment of vital signs and to a detailed examination of the cardiac, pulmonary, and neurologic systems.

Trauma is associated with use of cocaine can cause agitation, paranoia, distractibility, distorted perception, and depression. All of these may increase the likelihood of violence, suicide, or accidental injury.

THANK YOU
FOR YOUR ATTENTION