Clinical Toxicology

Antidepressant poisoning
Lec. 8

Dr Ahmed Salim Mahmood

Antidepressant (tricyclic)

Tricyclic antidepressants (TCA) are one of the common causes of a fatal drug overdose. They have a narrow therapeutic window so can be fatal at relatively lower doses and single tablet fatalities have been reported. Its most serious effects are cardiovascular and CNS instability. Patients have the potential to deteriorate quickly. Most poisoning presentations are from an acute ingestion; however chronic poisoning can also present acutely.

Tricyclic antidepressants : Amitriptyline; Imipramine; Nortriptyline; Doxepin and Clomipramine.

Toxic dose: Doses of less than 10 times the therapeutic daily dose may produce severe intoxication. In general, ingestion of 10–20 mg/kg is potentially life-threatening.

Mechanism of toxicity

Tricyclic antidepressant toxicity affects primarily the cardiovascular

and central nervous systems.

A. Cardiovascular effects. Several mechanisms contribute to cardiovascular toxicity:

1. **Anticholinergic effects** and inhibition of neuronal reuptake of catecholamines result in tachycardia and mild hypertension.
2. **Peripheral alpha-adrenergic blockade** causes vasodilation and contributes to hypotension.
3. **Membrane-depressant (quinidine-like)** effects cause myocardial depression and cardiac conduction disturbances by inhibition of the fast sodium channel. Metabolic or respiratory acidosis may contribute to cardiotoxicity by further inhibiting the fast sodium channel.

Mechanism of toxicity

Central nervous system effects: These effects result in part from anticholinergic toxicity (eg, sedation and coma), but seizures are probably a result of inhibition of reuptake of norepinephrine or serotonin in the brain or other central effects.

Clinical signs and symptoms

The peripheral ANS,CNS and heart are the main systems that are affected following overdose. Initial or mild symptoms typically develop within 2 hours and include tachycardia, drowsiness, a dry mouth, nausea , vomiting, urinary retention, confusion, agitation, and headache. More severe complications include hypotension, cardiac rhythm disturbances, hallucinations, and seizures. ECG abnormalities include sinus tachycardia and intraventricular conduction delay resulting in prolongation of the QRS complex and PR/QT intervals.

Diagnosis

- History about the amount of ingested, time of ingestion.
- Sings and symptom: Tricyclic antidepressant poisoning should be suspected in any patient with lethargy, coma, or seizures accompanied by ECG changes like QRS-interval prolongation or a terminal R wave in aVR of greater than 3 mm (typical sings)
- Serum level some time may be useful.

Treatment

Emergency and supportive measures

1. Maintain an open airway and assist ventilation if necessary

2. Treat coma, seizures, hyperthermia , hypotension, and arrhythmias if they occur.

Note: Do **not** use procainamide or other type Ia or Ic antiarrhythmic agents for ventricular tachycardia because these drugs may aggravate cardiotoxicity.

3. Consider cardiac pacing for bradyarrhythmias and high-degree AV block, and overdrive pacing for torsade de pointes.

4. If seizures are not immediately controlled with usual anticonvulsants, paralyze the patient with a neuromuscular blocker (Succinylcholine) to prevent hyperthermia, which may induce further seizures, and lactic acidosis, which aggravates cardiotoxicity.

6. Continuously monitor the temperature, other vital signs, and ECG in asymptomatic patients for a minimum of 6 hours.

Treatment

Specific drugs and antidotes

1. In patients with QRS-interval prolongation or hypotension, administer **sodium bicarbonate** (Sodium bicarbonate may reverse membrane-depressant effects by increasing extracellular sodium concentrations and by a direct effect of pH on the fast sodium channel.)
2. When cardiotoxicity persists despite treatment with sodium bicarbonate, the use of **lidocaine** can be considered. Lidocaine competes with tricyclic antidepressants for binding at the sodium channel but binds for a shorter period of time and thus may reverse some of sodium channel blockade.
3. For severe clomipramine overdose, the use of **intravenous lipid emulsion** therapy has been reported in case reports to be beneficial (sequester lipid soluble drug, provide energy for heart, stimlulate calcium channel in the heart and increase BP by stimulate alpha receptor)

Treatment

4. Hyperventilation, by inducing a respiratory alkalosis (or reversing respiratory acidosis), may also be of benefit but works only transiently and may provoke seizures.

5. Although **physostigmine** was advocated in the past, it should ***not*** be administered routinely to patients with tricyclic antidepressant poisoning; it may aggravate conduction disturbances, causing asystole; further impair myocardial contractility, worsening hypotension; and contribute to seizures.

Decontamination. Administer activated charcoal orally if conditions are appropriate. Gastric lavage , but it should be considered for large ingestions .

D. Enhanced elimination. Not useful because of large VD of most TCA.

MAO inhibitors antidepressant

Most monoamine oxidase (MAO) inhibitors are used primarily to treat severe depression but are also used to treat phobias and anxiety disorders. First-generation MAO inhibitors include **isocarboxazid**, **phenelzine** , and **tranylcypromine**. Newer-generation MAO inhibitors with lower toxicity include **selegiline** and rasagiline, also used in the treatment of Parkinson disease.

Mechanism of toxicity:

MAO inhibitors inactivate MAO, an enzyme responsible for degradation of catecholamines within CNS neurons. MAO is an enzyme with two major subtypes, MAO-A and MAO-B. MAO-A is also found in the liver and intestinal wall, where it metabolizes tyramine and therefore limits its entry into the systemic circulation. Toxicity results from the release of excessive neuronal stores of vasoactive amines, inhibition of metabolism of catecholamines, or absorption of large amounts of dietary tyramine (which in turn releases catecholamines from neurons).

Causes of toxicity by MAO inhibitors

Food interactions. Tyramine is a dietary monoamine that normally is degraded by gastrointestinal MAO-A. MAO inhibition allows excessive absorption of tyramine, which acts indirectly to release norepinephrine, causing a hyperadrenergic syndrome.

Interactions with indirectly acting monoamine drugs. Drugs that act indirectly to release norepinephrine, such as pseudoephedrine and phenylephrine, can cause marked hypertension and tachycardia. Selegiline is not likely to cause this reaction (MAO-B inhibitor in brain).

Acute overdose, which can contribute to hyperadrenergic symptoms in overdose.

Syrotonin syndrome Severe muscle hyperactivity, clonus, and hyperthermia may occur when patients receiving MAO inhibitors use even therapeutic doses of drugs such as meperidine, tramadol, dextromethorphan, tricyclic antidepressants, SSRIs, venlafaxine, methylene blue, tryptophan

Sings and symptoms

Symptoms may be delayed 6–24 hours after acute overdose but occur rapidly after ingestion of interacting drugs or foods in a patient on chronic MAO inhibitor therapy. Because of irreversible inactivation of MAO, toxic effects (and the potential for drug or food interactions) may persist for several days when first-generation drugs are involved.

Signs and symptoms

Drug or food interactions	serotonin syndrome	Acute over dose
Tachycardia, hypertension, flushing, and headache. Hypertensive crisis can lead to ischemia and end-organ damage such as intracranial hemorrhage, MI or renal failure.	Hyperthermia, tremor, myoclonic jerking, hyperreflexia, and shivering . Lower extremity clonus	Severe hypertension, delirium, hyperthermia, dysrhythmias, seizures, and hypotension and cardiovascular collapse with multisystem failure. Mydriasis, nystagmus, hallucinations, and tachypnea.

Diagnosis

1. Diagnosis is based on clinical features of sympathomimetic drug intoxication.
2. History of MAO inhibitor use, particularly in combination with drugs or foods known to interact.
3. Other useful laboratory studies include electrolytes, glucose, BUN, creatinine, creatine kinase (CK), troponin, 12-lead ECG, and ECG monitoring. If intracranial hemorrhage is suspected, perform a CT head scan.

Treatment

1. Maintain ABC
2. Treat hypertension, coma, seizures, and hyperthermia if they occur.
3. Use titratable intravenous antihypertensives such as nitroprusside and phentolamine because of the potential for rapid changes in hemodynamics.
4. If hypotension occurs, norepinephrine is preferred
5. Specific drugs and antidotes: Because the hypertension is catecholamine-mediated, alpha-adrenergic blockers (eg, phentolamine) or combined alpha- and beta-adrenergic blockers (eg, labetalol) are particularly useful.
6. Serotonin syndrome should be treated with supportive care, sedation, and cooling. Cyproheptadine (Periactin), and Chlorpromazine 25–50 mg IV has also been used.
7. Administer activated charcoal orally or doing of gastric lavage if conditions are appropriate

SSRI Toxicity

Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressants. Other clinical indications for SSRI use include anxiety disorders, obsessive-compulsive disorder, panic disorders, and eating disorders. Compared to their predecessors, the monoamine oxidase inhibitors and tricyclic antidepressants, SSRIs are associated with fewer toxic effects.

SSRI include: Citalopram, Escitalopram , Fluoxetine ,Paroxetine Sertraline , Duloxetine , Venlafaxine, Bupropion and Mirtazapine

SSRI Toxicity

Signs and symptoms: like the TCA and MAO inhibitors but its mainly serotonin syndrome

Treatment:

Like guideline of TCA poisoning and the serotonin syndrome is managed with cyproheptadine, an antihistaminic drug used as an antiserotonergic agent in this situation—a dose of 4 to 8 mg orally, repeated every 2 hours until a favorable response is noted, followed by 4 mg orally every 6 hours for 48 hours.

Case study

- A 21-year-old female with a history of generalized anxiety disorder and major depression presented with increased depressive symptoms over several months while taking fluoxetine 20 mg daily. Fluoxetine was discontinued without taper and replaced with paroxetine 10 mg daily, along with hydroxyzine 50 mg twice daily as needed for anxiety. Within a week of starting the paroxetine, the patient reported increased anxiety, insomnia, and constant shaking. The paroxetine continued to be uptitrated over a 3-week period to a dose 30 mg due to unremitting depressive symptoms. One month later, the patient presented with tachycardia, generalized body aches, extreme fatigue, weakness, uncontrollable twitching, tremor, and hyperreflexia. A widespread burning sensation accompanied by random hot flashes without diaphoresis was also noted. Serotonin syndrome was diagnosed using the Hunters criteria. Paroxetine was discontinued, and the patient's physical symptoms resolved within a week.


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