Clinical Toxicology

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Sedative-Hypnotics Toxicity

- **Sedative:** Calm down, treat agitation

- **Hypnotic:** Induce sleep

  -go to sleep fast, feel refreshed tomorrow !!!

- **Anxiolytic:** Reduce anxiety

  - physical, emotional, cognitive

Benzodiazepines Toxicity

The drug class of benzodiazepines includes many compounds that vary widely in potency, duration of effect, presence or absence of active metabolites, and clinical use. Three nonbenzodiazepines—eszopiclone, zaleplon, and zolpidem— have similar clinical effects and are included here. In general, death from benzodiazepine overdose is rare unless the drugs are combined with other CNS-depressant agents, such as ethanol, opioids, and barbiturates. Newer potent, short-acting agents have been considered the sole cause of death in recent forensic cases.

Benzodiazepines Toxicity

Mechanism of toxicity. Benzodiazepines enhance the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The result is generalized depression of spinal reflexes and the reticular activating system. This can cause coma and respiratory arrest.

A. Respiratory arrest is more likely with newer short-acting benzodiazepines such as triazolam , alprazolam (Xanax), and midazolam . It has also been reported with zolpidem .

B. Cardiopulmonary arrest has occurred after rapid injection of diazepam, possibly because of CNS-depressant effects or because of the toxic effects of the diluent propylene glycol.

Toxic dose Benzodiazepines

In general, the toxic-therapeutic ratio for benzodiazepines is very high. For example, oral overdoses of diazepam have been reported in excess of 15–20 times the therapeutic dose without serious depression of consciousness. However, respiratory arrest has been reported after ingestion of 5 mg of triazolam and after rapid IV injection of diazepam, midazolam, and many other benzodiazepines. Also, ingestion of another drug with CNS-depressant properties (eg, ethanol, barbiturates, opioids) probably will produce additive effects.

Clinical presentation

Onset of CNS depression may be observed within 30–120 minutes of ingestion, depending on the compound. Lethargy, slurred speech, ataxia, coma, and respiratory arrest may occur. Generally, patients with benzodiazepine-induced coma have hyporeflexia and mid-position or small pupils. Hypothermia may occur. Serious complications are more likely when newer short-acting agents are involved or when other depressant drugs have been ingested.

Diagnosis

Diagnosis usually is based on the history of ingestion or recent injection. The differential diagnosis should include other sedative-hypnotic agents, antidepressants, antipsychotics, and narcotics. Coma and small pupils do not respond to naloxone but will reverse with administration of flumazenil.

Measurement the level of the drug in urine and blood qualitative screening may provide rapid confirmation of exposure.

Benzodiazepines

Interactions

Increased Effects with

- Alcohol
- Analgesics (Fentanyl)
- Antibacterial (Clarithromycin, Isoniazid)
- Antifungals (ketokonazole, itraconazole)
- Antipsycotics
- Antivirals
- Muscle relaxants (baclofen)

Decreased Effects with

- Antibacterial (Rifampicin)
- Probenecid
- Theophylline

Benzodiazepines

Caution with Benzodiazepines
Reduce dose with:

- Elderly or weakened.
- Acute alcohol intoxication.
- Acute angle glaucoma.
- COPD.

Treatment of Benzodiazepines Tox.

1. Emergency and supportive measures (Protect the airway and assist ventilation if necessary).
2. Treat coma, hypotension, and hypothermia if they occur. Hypotension usually responds promptly to supine position and IV fluids.
3. Use specific antidote (Flumazenil).
4. Activated charcoal if the ingestion occurred within the previous 30 minutes. Gastric lavage is not necessary.
5. There is no role for diuresis, dialysis, or hemoperfusion.

Flumazenil

Flumazenil is a specific benzodiazepine receptor antagonist that can rapidly reverse coma. However, because benzodiazepine overdose by itself is rarely fatal, the role of flumazenil in routine management has not been established.

Dose and rout of administration: It is administered IV with a starting dose of 0.1–0.2 mg, repeated as needed up to a maximum of 3 mg.

Side effects of flumazenil

1. It may induce seizures in patients who have co-ingested medications with proconvulsant activity.
2. It may induce acute withdrawal, including seizures and autonomic instability, in patients who are addicted to benzodiazepines.
3. Re-sedation is common when the drug wears off after 1–2 hours, and repeated dosing or a continuous infusion is often required.

Barbiturates toxicity

Barbiturates have been used as hypnotic and sedative agents, for the induction of anesthesia, and for the treatment of epilepsy and status epilepticus. They have been largely replaced by newer drugs. They often are divided into four major groups according to their pharmacologic activity and clinical use: **ultra-short-acting,**

- **short-acting,**
- **intermediate-acting,**
- and **long-acting**

Mechanism of toxicity

All barbiturates cause generalized depression of neuronal activity in the brain. Interaction with a barbiturate receptor leads to enhanced gamma-aminobutyric acid (GABA)–mediated chloride currents and results in synaptic inhibition. Hypotension that occurs with large doses is caused by depression of central sympathetic tone as well as by direct depression of cardiac contractility.

Toxic dose of barbiturate

The toxic dose of barbiturates varies widely and depends on the drug, the route and rate of administration, and individual patient tolerance. In general, toxicity is likely when the dose exceeds 5–10 times the hypnotic dose. Chronic users or abusers may have striking tolerance to depressant effects.

A. The potentially fatal **oral dose** of the shorter-acting agents such as pentobarbital is 2–3 g, compared with 6–10 g for phenobarbital.

B. Several deaths were reported in young women undergoing therapeutic abortion after they received rapid **IV injections** of as little as 1–3 mg of methohexital per kilogram.

Clinical presentation

The onset of symptoms depends on the drug and the route

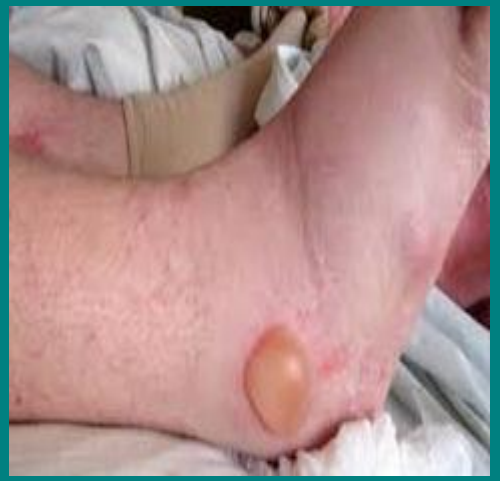
of administration.

A. Lethargy, slurred speech, nystagmus, and ataxia are common with mild to moderate intoxication. With higher doses, hypotension, coma, and respiratory arrest commonly occur. With deep coma, the pupils are usually small or mid-position; the patient may lose all reflex activity and appear to be dead.

B. Hypothermia is common in patients with deep coma, especially if the victim has been exposed to a cool environment. Hypotension and bradycardia commonly accompany hypothermia.

Diagnosis of barbiturate toxicity

Diagnosis is usually based on a history of ingestion and should be suspected in any epileptic patient with stupor or coma. Although skin bullae blisters sometimes are seen with barbiturate overdose, they are not specific for barbiturates. Other causes of coma should also be considered.



Measurement the level of barbiturate in the serum and urine is important in diagnosis.

Treatment of Barb. toxicity

1. Emergency and supportive measures should be done (As with Benzodiazepam)
2. There is no specific antidote.
3. Administer activated charcoal orally if conditions are appropriate.
4. Enhanced elimination by alkalinization of the urine increases the urinary elimination of phenobarbital but not other barbiturates. Its value in acute overdose is unproven, and it may potentially contribute to fluid overload and pulmonary edema.
5. Repeat-dose activated charcoal has been shown to decrease the half-life of phenobarbital and its metabolites.
6. Continuous venovenous hemodiafiltration has been reported to accelerate elimination.

Chloral hydrate

- Chloral hydrate is oral soluble liquid. It is metabolized to trichloroethanol, which is responsible for CNS depressant activity. In addition, trichloroethanol may sensitize the myocardium to the effects of catecholamines, resulting in cardiac arrhythmias.

Acute overdose is often characterized by nausea, vomiting, confusion, convulsions, slow and irregular breathing, cardiac arrhythmia, and coma.

- Chloral hydrate is radiopaque and may be visible on plain abdominal radiographs.
- Accidental over dosage of young children undergoing simple dental or surgical procedures has occurred.
- Hemodialysis has been used successfully to accelerate clearance of the drug in poisoning victims.
- Treatment is supportive and include treatment of dysthrmia.

Propofol

- Propofol is used for procedural sedation and either induction or maintenance of general anesthesia.
- It is highly lipid soluble, so it crosses the blood–brain barrier rapidly.
- Propofol causes dose-related respiratory depression.
- Propofol may decrease systemic arterial pressure and cause myocardial depression.
- Prolonged propofol infusions for more than 48 hours at rates of 4–5 mg/kg/h or greater are associated with a life-threatening propofol infusion syndrome (PIS) involving metabolic acidosis, cardiac dysrthythmias, and skeletal muscle injury.
- There is no reversal agent for propofol. Adverse effects must be treated until the drug is metabolized.
- Support the ventilation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