

# Barbiturates and Benzodiazepines

# Barbiturates

- Barbiturates are used as hypnotic and sedative agents, for the induction of anesthesia, and for the treatment of epilepsy and status epilepticus.

Drug	Normal Terminal Elimination Half-Life (h)	Usual Duration of Effect (h)	Usual Hypnotic Dose (Adult) (mg)	Toxic Level (mg/L)
<b>Ultrashort-acting</b>				
Methohexital	3–5	< 0.5	50–120	>5
Thiopental	8–10	< 0.5	50–75	>5
<b>Short-acting</b>				
Pentobarbital	15–50	> 3–4	50–200	>10
Secobarbital	15–40	> 3–4	100–200	>10
<b>Intermediate-acting</b>				
Amobarbital	10–40	> 4–6	65–200	>10
Aprobarbital	14–34	> 4–6	40–160	>10
Butobarbital	35–50	> 4–6	100–200	>10
Butalbital	35		100–200	>7
<b>Long-acting</b>				
Mephobarbital	10–70	> 6–12	50–100	>30
Phenobarbital	80–120	> 6–12	100–320	>30

# 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

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

# Clinical presentation

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

# Diagnosis

- It is usually based on a history of ingestion and should be suspected in any epileptic patient with stupor or coma.
- Specific levels
  - Serum drug levels

# Treatment

## **A. Emergency and supportive measures**

- Protect the airway and assist ventilation if necessary.
- Treat coma, hypothermia, and hypotension if they occur

## **B. Specific drugs and antidotes.**

- There is no specific antidote.

## **C. Decontamination**

- Prehospital.
  - Administer activated charcoal, if available.
- Hospital.
  - Administer activated charcoal. Consider gastric lavage for massive ingestion.



## **D. Enhanced elimination**

**Alkalinization** of the urine increases the urinary elimination of phenobarbital but not other barbiturates. It may potentially contribute to fluid overload and pulmonary edema.

**Repeat-dose activated charcoal** has been shown to decrease the half-life of phenobarbital.

**Hemoperfusion or hemodialysis** may be necessary for severely intoxicated patients not responding to supportive care

# Benzodiazepines

- In general, death from benzodiazepine overdose is rare, unless the drugs are combined with other CNS-depressant agents such as ethanol or barbiturates.

Drug	Half-Life (h)	Active Metabolite	Oral Adult Dose (mg)
Alprazolam	6.3–26.9	No	0.25–0.5
Chlordiazepoxide	40–120 <sup>a</sup>	Yes	5–50
Clonazepam	18–50	No	0.5–2
Clorazepate	40–120 <sup>a</sup>	Yes	3.75–30
Diazepam	40–120 <sup>a</sup>	Yes	5–20
Estazolam	8–28	No	1–2
Flunitrazepam	20	Yes	1–2
Flurazepam	47–100 <sup>a</sup>	Yes	15–30
Lorazepam	10–20	No	2–4
Midazolam	2.2–6.8	Yes	1–5 <sup>b</sup>
Oxazepam	5–20	No	15–30
Quazepam	70–75 <sup>a</sup>	Yes	7.5–15
Temazepam	3.5–18.4	No	15–30
Triazolam	1.5–5.5	No	0.125–0.5
Zaleplon <sup>c</sup>	1	No	5–20
Zolpidem	1.4–4.5	No	5–10

# 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
- Respiratory arrest is more likely with newer short-acting benzodiazepines such as triazolam, alprazolam, and midazolam
- 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

- 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.

# 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

- It is usually based on the history of ingestion
- Specific levels
- Serum drug levels are often available

# Treatment

## **A. Emergency and supportive measures**

- Protect the airway and assist ventilation if necessary
- Treat coma, hypotension, and hypothermia if they occur.
- Hypotension usually responds promptly to supine position and intravenous fluids.

## B. Specific drugs and antidotes.

- 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 yet to be established.
- It is administered intravenously with a starting dose of 0.1–0.2 mg, repeated as needed up to a maximum of 3 mg.
- It has some important potential drawbacks
  - It may induce seizures in patients with tricyclic antidepressant overdose.
  - It may induce acute withdrawal, including seizures and autonomic instability, in patients who are addicted to benzodiazepines.
  - Resedation is common when the drug wears off after 1–2 hours, and repeated dosing or a continuous infusion is often required



## C. Decontamination

- Prehospital.
  - Administer activated charcoal if available.
- Hospital.
  - Administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly

## D. Enhanced elimination.

- There is no role for diuresis, dialysis, or hemoperfusion.
- Repeat-dose charcoal has not been studied.



















