IN THE NAME OF GOD

BARBITURATE AND ANTI-EPILEPTIC INTOXICATION

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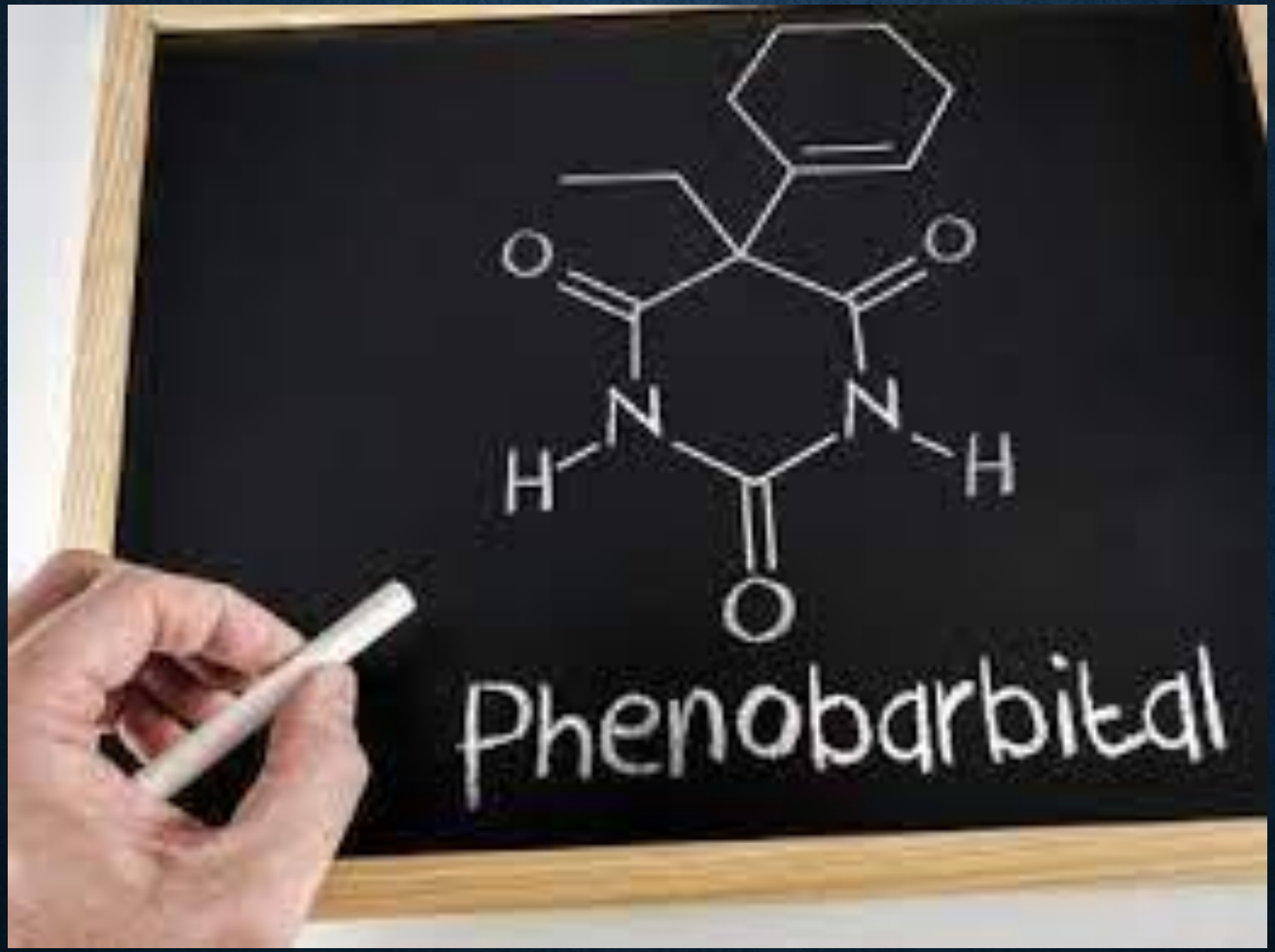
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Phenobarbital

- Status epilepticus, severe ethanol and sedative withdrawal syndromes,and toxicologic seizures are typically managed with benzodiazepines, but barbiturates have a useful role as second-line agents.
- They are still used in combination drugs (e.g., butalbital) and alone (e.g., secobarbital) for the treatment of tension and migraine headaches and for refractory intracranial hypertension from focal and diffuse brain injury.

- Barbiturates are generally classified to their duration of action
- Dependent on lipid solubility and tissue distribution rather than the elimination half-life

TABLE 182-1 Selected Properties of Commonly Used Barbiturates in Adults

	Long Acting*	Intermediate Acting*		Short Acting*		Ultrashort Acting*	
Agent	Phenobarbital†	Amobarbital	Butalbital	Pentobarbital	Secobarbital	Thiopental	Methohexital
Duration of action (hours)	>6	3–6	3–4	<3	<3	5–10 min	5–7 min
Elimination half-life (hours)	24–96	14–42	35–88	21–42	20–28	6–26	1–2
Hypnotic dose PO (milligrams)	300–500	100–200	50–200	100–200	50–100	100–200	50–100 IV
Fatal dose, approximate (grams)‡	5	3–6	2–5	3–6	3–6	ND	ND

- Barbiturates readily distribute throughout the body to most tissues
- Crossing the blood–brain barrier and placenta
- Excreted in breast milk.
- Fetal blood barbiturate concentrations closely reflect maternal plasma levels, creating the potential for fetal withdrawal syndrome.

- Metabolized in the liver to inactive metabolites
- The elimination half-life of barbiturates can be greatly shortened in infants and children and very prolonged in the elderly and in patients with liver or renal disease.
- Chronic barbiturate use accelerate the metabolism of concurrently taken therapeutic drugs such as oral contraceptives, anticoagulants, and corticosteroids.

- Blockade of the calcium channel may contribute to the cardiac contractility impairment seen with barbiturate overdoses.

CLINICAL FEATURES

- ***Mild to moderate*** barbiturate intoxication closely resembles alcohol intoxication and toxicity of other sedative-hypnotics.
- Drowsiness
- Disinhibition
- Ataxia
- Slurred speech
- Mental confusion

- ***severe* barbiturate intoxication**
- The progressive neurologic depression from stupor to coma to complete neurologic unresponsiveness, including the absence of a corneal reflex, deep tendon reflexes, and even brainstem reflexes (in patients who ultimately completely recover)

- **Vital sign abnormalities**
- Respiratory depression
- Hypothermia
- Hypotension, with respiratory depression usually occurring first
- Pulse rate, pupil size, light reactivity, and nystagmus are variable

- GI tract motility is slowed, resulting in delayed gastric emptying and ileus.
- **Skin bullae**, sometimes referred to as “barb blisters” or “coma blisters,”

- Early **deaths** in barbiturate overdose result from respiratory arrest and cardiovascular collapse.
- Common **complications** include:
- Hypoglycemia (perhaps due to starvation)
- Pulmonary edema
- Aspiration pneumonia
- Acute lung injury.
- Current mortality rates range between 1% and 3%; death usually results from multiple organ system failure.

DIAGNOSIS

- Glucose levels
- Blood chemistries, CBC, blood gas (if indicated), toxicology screen for co-ingestants, chest radiograph, and an ECG.
- Urine drug screens most commonly use the immunoassay methodology, and a false-positive result on the barbiturate screen has been reported with ibuprofen and naproxen

- Barbiturate serum levels are useful in establishing the diagnosis of a comatose patients
- Acute treatment decisions should be clinically based.
- Measurements are not reliable in predicting clinical course after an overdose because they do not reflect brain barbiturate concentrations and may underestimate the clinical condition of a patient in the setting of polydrug exposure.
- Barbiturate levels are also invalid in chronic barbiturate abusers who have developed physiologic tolerance and in patients with renal or hepatic disease who have decreased clearance

TREATMENT

- The initial priorities are airway management and supportive care.
- Once pulmonary and cardiovascular function has been stabilized, options for increasing drug clearance are considered

AIRWAY ASSESSMENT AND INITIAL STABILIZATION

- Intubation with mechanical ventilation in severe sedative-hypnotic overdose
- Decreased cardiac output and vascular tone, often resulting in profound hypotension. Volume expansion with IV crystalloids in the absence of cardiac failure.
- If fluid resuscitation fails to correct hypotension, administer vasopressors such as dopamine or norepinephrine.
- Hypothermia between 30°C (86°F) and 36°C (96.8°F) is common and should be monitored via continuous core temperature and treated with rewarming measures.

ACTIVATED CHARCOAL

- A single dose of activated charcoal should be given to cooperative, clinically stable patients who present within 1 hour of acute oral overdose.
- Multidose activated charcoal if a patient has ingested a life-threatening amount of phenobarbital.
- A typical adult regimen for multidose activated charcoal is an initial dose of 50 to 100 grams PO followed by 12.5 to 25 grams PO every 4 hours.
- Concurrent administration of cathartic agents remains unproven and is discouraged
- Careful attention to and monitoring of the patient's airway is important to decrease the risk of aspiration or bowel obstruction

FORCED DIURESIS AND URINARY ALKALIZATION

- Forced diuresis is **not recommended** because of the risks of sodium and fluid overload and lack of proven efficacy.
- Urinary alkalization does enhance the clearance of phenobarbital and primidone (which is metabolized to phenobarbital).
- This treatment is less effective than multidose activated charcoal in reducing serum levels, does not improve clinical outcomes, and **is not effective for shorter-acting barbiturates**.
- In barbiturate poisoning, urinary alkalization is not a first-line treatment and has only a minor, if any, role

EXTRACORPOREAL ELIMINATION

- Hemodialysis, hemoperfusion, and hemodiafiltration can enhance elimination of phenobarbital, but are reserved for patients who are deteriorating despite aggressive supportive care.
- **These modalities are not useful for poisoning from barbiturates other than phenobarbital.**
- Exchange transfusion has also been reported to be useful in neonatal phenobarbital toxicity.

DISPOSITION AND FOLLOW-UP

- Mild to moderate barbiturate intoxication responds well to general supportive care, including a single dose of activated charcoal
- Improvement in neurologic status and vital signs over 6 to 8 hours signals eventual patient discharge or transfer.
- For a long-acting agent such as phenobarbital, serial serum levels should be obtained during the initial 6 hours after an overdose before concluding the patient can be safely discharged or transferred.
- Evidence of toxicity after 6 hours will require hospital admission, and patients with severe toxicity should go to the intensive care unit.
- Consult with a medical toxicologist or local poison center to assist in the care of severe barbiturate-poisoned patients

BARBITURATE WITHDRAWAL SYNDROME

- Symptoms similar to alcohol or benzodiazepine withdrawal.
- Range from anxiety and restlessness to hallucinations, delirium, and/or generalized seizures.
- Severe symptoms in the ED can be treated with benzodiazepines or barbiturates, but due to the associated mortality, gradual in-hospital detoxification is needed.

PHENYTOIN AND FOSPHENYTOIN

- Partial and generalized tonic-clonic seizures.
- Non–drug-induced status epilepticus.
- Prevent seizures due to head trauma (in the immediate posttraumatic period)
- Management of some chronic pain syndromes.
- Serious complications are extremely rare after intentional phenytoin overdose if supportive care is provided.
- Most phenytoin-related deaths have been associated with rapid IV administration or hypersensitivity reactions.


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HYDANTIC®
Phenytoin sodium 250mg/5ml
Each ampoule (5ml) contains:
Phenytoin sodium 250mg
Only Slow IV injection (1 ml/min)
See the enclosed leaflet for details.
Store below 30°C.
Protect from light and freezing.
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- **Phenytoin** is available in oral and injectable forms.
- Phenytoin has poor solubility in water, so the vehicle for the parenteral formulation is 40% propylene glycol and 10% ethanol, adjusted to a pH of 12 with sodium hydroxide.
- The acute cardiovascular toxicity seen with IV phenytoin infusion is usually ascribed to the propylene glycol diluent.

- **Fosphenytoin** (a disodium phosphate ester of phenytoin) is a prodrug that is converted to phenytoin by phosphatases in the body with a conversion half-life of 10 to 15 minutes.
- **The advantage of parenteral fosphenytoin is that it is soluble in aqueous solutions, is buffered to a pH of 8.8, is nonirritating to the tissues, and can be given by IM injection**

CLINICAL FEATURES

- **CNS Toxicity** :inhibitory cortical and excitatory cerebellar and vestibular effects
- The initial sign of toxicity is usually nystagmus, which is seen first on forced lateral gaze and later becomes spontaneous Vertical, bidirectional, or alternating nystagmus
- Decreased level of consciousness ,lethargy, ataxic gait, and dysarthria.
- This may progress to confusion, coma, and even apnea in a substantial overdose.
- Complete ophthalmoplegia and loss of corneal reflexes

- **Phenytoin-induced seizures** are usually brief and generalized; they are almost always preceded by other signs of toxicity, especially in acute overdose.
- **Acute dystonias** and movement disorders such as opisthotonos and choreoathetosis.
- Hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited.
- Chronic neurologic toxicity includes peripheral neuropathy and cerebellar degeneration with ataxia

- **Cardiovascular Toxicity**
- **Entirely limited to cases of IV administration, in large part due to the constituents of the parenteral vehicle or, in rare cases, with chronic oral toxicity.**
- Hypotension with decreased peripheral vascular resistance
- Bradycardia, conduction delays progressing to complete atrioventricular nodal block, ventricular tachycardia, primary ventricular fibrillation, and asystole.

- **ECG changes:**increased PR interval, widened QRS interval, and altered ST segments and T waves.
- More common in the elderly, those with underlying cardiac disease, and the critically ill.
- Parenteral phenytoin administration:a slow rate of infusion and constant monitoring.
- Even though fosphenytoin does not contain the propylene glycol diluent, cardiovascular toxicity can occur with IV administration.

- **Vascular and Soft Tissue Toxicity:**
- IV extravasation can produce skin and soft tissue necrosis, compartment syndrome, and limb gangrene.
- Delayed bluish discoloration of the affected extremity (“purple glove syndrome”) followed by erythema, edema, vesicles, bullae, and local tissue ischemia.

- **Hypersensitivity Reactions**
- within 1 to 6 weeks of beginning phenytoin therapy,febrile illness with skin changes (erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis) and internal organ involvement (hepatitis, rhabdomyolysis, acute interstitial pneumonitis, renal failure, lymphadenopathy, leukopenia, and/or disseminated intravascular coagulation).
- **Patients with a history of previous hypersensitivity reactions should not receive phenytoin, and because of similar reactions to phenobarbital, lamotrigine, felbamate, and carbamazepine, these anticonvulsants should also be avoided**

TREATMENT

- Correct acidosis (respiratory or metabolic) to decrease the active free phenytoin fraction.
- Multidose activated charcoal may decrease drug half-life, but does not decrease time to recovery and does not change outcome in overdose patients.
- Seizures may be treated with IV benzodiazepines or phenobarbital, with the caution that seizures are uncommon in phenytoin overdose.
- **For patients with severe and persistent toxicity, hemodialysis and hemoperfusion can produce substantial improvement in neurologic toxicity**

- **Cardiac monitoring after isolated oral ingestion is unnecessary.**
- Atropine and temporary cardiac pacing may be used for symptomatic bradyarrhythmias associated with IV phenytoin.
- Hypotension that occurs during IV administration of phenytoin or fosphenytoin usually responds to discontinuation of the infusion and administration of isotonic crystalloid.

DISPOSITION AND FOLLOW-UP

- **Phenytoin has a long and erratic absorption phase after oral overdose, so the decision to discharge or medically clear a patient for psychiatric evaluation cannot be based on one serum level.**
- After acute ingestions, serum level should be measured every few hours.
- Patients with oral ingestion who have serious complications (seizures, coma, altered mental status, or significant ataxia) should be admitted for further evaluation and treatment.
- Those with mild symptoms should be observed in the ED and discharged once their levels of phenytoin are declining and they are clinically well.
- Mental health or psychiatric evaluation should be obtained, as indicated, in cases of intentional overdose.

VALPROIC ACID

- Valproic acid (oral preparation) or valproate sodium (IV form) is used to treat tonic-clonic seizures, absence seizures, partial complex seizures, and posttraumatic epilepsy,migraine headache prophylaxis, to control manic episodes in bipolar disorder, and in the treatment of neuropathic pain.

CLINICAL FEATURES

- CNS depression(drowsiness to coma)
- Respiratory depression, hypotension, hypoglycemia, hypocalcemia, hypernatremia, hypophosphatemia, and anion gap metabolic acidosis
- Elevated serum levels of aminotransferases, ammonia, and lactate
- Pancreatitis may occur, and thrombocytopenia may be clinically significant and severe

- Cerebral edema
- Valproic acid–induced hepatotoxicity ,intrinsic and benign (reversible, reproducible, and dose dependent) or idiosyncratic and fatal (unpredictable, not dose dependent, with a long latent period)
- Children <3 years of age at highest risk for fatal hepatotoxicity, with an incidence of about 1 in 500.
- Serum levels of transaminases and ammonia should be checked in children on valproate therapy who demonstrate somnolence or lethargy

DIAGNOSIS

- Therapeutic valproic acid concentrations are 50 to 100 micrograms/mL (346 to 693 micromole/L).
- Although serum concentration does not correlate well with either seizure control or toxicity, adverse side effects increase as concentrations rise above 150 micrograms/mL (1040 micromole/L), and coma may occur with levels above 800 micrograms/mL (5547 micromole/L).
- Serum ammonia and glucose concentrations should be measured with suspected valproic acid toxicity.
- **Valproic acid is eliminated partly as ketone bodies and may cause a positive test result for ketones in the urine or blood.**

TREATMENT

- Single-dose activated charcoal
- Consider multidose activated charcoal and/or whole-bowel irrigation after ingestion of enteric-coated, delayed-release preparations

- Overdose patients have been given **l-carnitine** in an attempt to increase valproic acid metabolism by beta oxidation
- In cases of valproic acid toxicity with lethargy, coma, hyperammonemia, and hepatic dysfunction

- **Hemoperfusion and hemodiafiltration**
- Unbound (free) drug is markedly increased in overdose, and removal of valproic acid from this pool appears beneficial
- During hemoperfusion and hemodiafiltration treatment, elimination half-life is decreased by two- to seven-fold

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