

Barbiturates

Last updated: September 5, 2017

MECHANISM OF ACTION	1
PHARMACOLOGIC ACTIONS	1
PHARMACOKINETICS	1
THERAPEUTIC USES	1
ADVERSE EFFECTS	1
BARBITURATE OVERDOSE	1

MECHANISM OF ACTION

- At **low doses** - **potentiation of GABA action on Cl⁻ channel**; barbiturates presumably bind to *PICROTOXIN BINDING SITE*.
N.B. barbiturates do not bind to *BENZODIAZEPINE RECEPTORS*!
- At **higher doses** - **interference with Na⁺ and K⁺ transport across cell membranes** → generalized inhibition of polysynaptic transmission in all CNS areas (esp. mesencephalic ARAS).
N.B. barbiturates are less selective than benzodiazepines!

PHARMACOLOGIC ACTIONS

- nonspecific generalized **CNS depression** in dose-dependent fashion: sedation → hypnosis → anesthesia → coma → death.

- respiratory depression** (barbiturates suppress respiration at various levels – CNS and chemoreceptor) up to death.
- vasomotor medullary center depression** occurs only at toxic doses.
- PHENOBARBITAL** has specific **anticonvulsant activity** different from nonspecific CNS depression. see p. E3 >>
- in anesthetic doses, barbiturates significantly **decrease CNS O₂ utilization**.

No analgesic properties (at low doses, even exacerbate pain!); *anxiolytic properties* much lower than of benzodiazepines!

PHARMACOKINETICS

- absorbed **orally**.
- distributed widely throughout body; *all barbiturates redistribute**: brain → splanchnic areas → skeletal muscle → adipose tissue.
*cause of short duration of action of (ultra-)short-acting derivatives!!!
- higher lipid solubility → more rapid onset & shorter duration of action, higher potency.
- metabolized in **liver**; inactive metabolites excreted in **urine**.
- duration of action** is very important clinically - determines therapeutic use:

LONG-ACTING barbiturates (T_{1/2} – 1-2 days) – used as **antiepileptics**.

PHENOBARBITAL - duration of action greater than day. see p. E3 >>

BARBITAL

SHORT-ACTING barbiturates (T_{1/2} – 2-8 hours) – used rarely as **sedative-hypnotics** or **anxiolytics**.

PENTOBARBITAL – used to induce **therapeutic coma** in refractory status epilepticus.

SECOBARBITAL

AMOBARBITAL

HEXOBARBITAL

BUTABARBITAL

ULTRA SHORT-ACTING barbiturates (T_{1/2} – 20 minutes) – used for **anesthesia induction**.

THIOPENTAL - acts within seconds; duration of action ≈ 30 minutes.

THERAPEUTIC USES

- Intravenous **anesthesia induction** - *ultra-short-acting* barbiturates (**THIOPENTAL**).
- Anticonvulsant** - *long-acting* barbiturates (**PHENOBARBITAL**): see p. E3 >>
 - status epilepticus in children
 - eclampsia
 - young children with recurrent febrile seizures (**PHENOBARBITAL** is drug of choice).
- Mild **sedatives** (to relieve anxiety, insomnia) - *short-acting* barbiturates (were formerly mainstay, but now have been largely replaced by benzodiazepines).
 - barbiturates decrease amount of REM sleep (as do benzodiazepines); after drug discontinuance - rebound of REM sleep (usually in form of nightmares).
- Producing therapeutic **barbiturate coma** for CNS protection (via reduction of O₂ utilization).
- Kernicterus treatment** in neonates (via P-450 induction).

ADVERSE EFFECTS

- CNS depression** (drowsiness, impaired concentration, mental and physical sluggishness).
- Drug hangover (residual CNS depression)** - feeling of tiredness (± nausea and dizziness) for many hours after patient awakes.
- High potential for **physical dependence & addiction** (abrupt withdrawal → severe tremors, anxiety, weakness, restlessness, nausea & vomiting, grand mal seizures, delirium with vivid hallucinations, cardiac arrest).

Withdrawal is much more severe than opiate withdrawal and can result in **DEATH!!!**

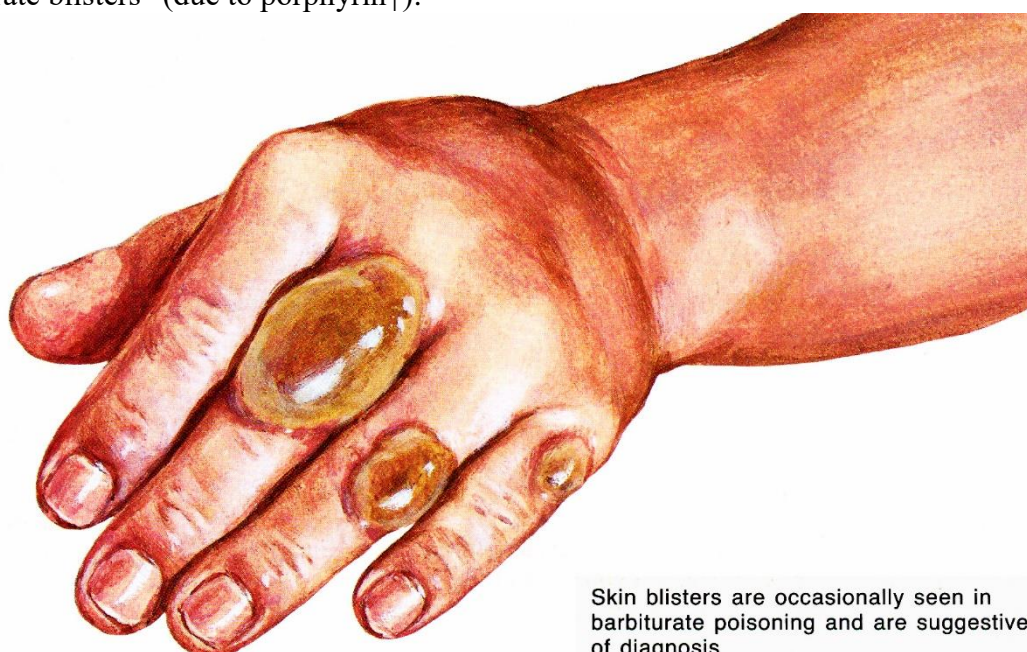
- P-450 microsomal enzyme induction**:
 - diminished action of drugs that are dependent on P-450 metabolism (incl. quickly developing **tolerance** to barbiturate itself!!!).
 - increased porphyrin synthesis (barbiturates are contraindicated in acute intermittent porphyria).
- Narrow therapeutic index** → frequent overdoses.

BARBITURATE OVERDOSE

- leading cause of death among drug overdoses.

- metabolic coma** with severe **respiratory & cardiovascular** depression. also see p. Psy23 >>
- short-acting preparations are more lethal at lower doses.

- patient who survives acute episode may develop bronchopneumonia, renal tubular acidosis, cutaneous “barbiturate blisters” (due to porphyrin↑):



Skin blisters are occasionally seen in barbiturate poisoning and are suggestive of diagnosis

Source of picture: Frank H. Netter “Clinical Symposia”; Ciba Pharmaceutical Company; Saunders >>

- treatment: *no specific antidotes!*
 - 1) artificial respiration + cardiovascular support
 - 2) stomach purging
 - 3) urine alkalinization (barbiturates are acidic)
 - 4) **hemodialysis** – most effective treatment!!!

BIBLIOGRAPHY for “Barbiturates” → follow this [LINK >>](#)