Barbiturates

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MECHANISM OF ACTION

1. 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*!
2. 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 O_2 utilization**.

No analgesic properties (al 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

1. Intravenous **anesthesia induction** - *ultra-short-acting* barbiturates (THIOPENTAL).
2. **Anticonvulsant** - *long-acting* barbiturates (PHENOBARBITAL): see p. E3 >>
   1) status epilepticus in children
   2) eclampsia
   3) young children with recurrent febrile seizures (PHENOBARBITAL is drug of choice).
3. 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).
4. Producing therapeutic **barbiturate coma** for CNS protection (via reduction of O_2 utilization).
5. **Kernicterus treatment** in neonates (via P-450 induction).

ADVERSE EFFECTS

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

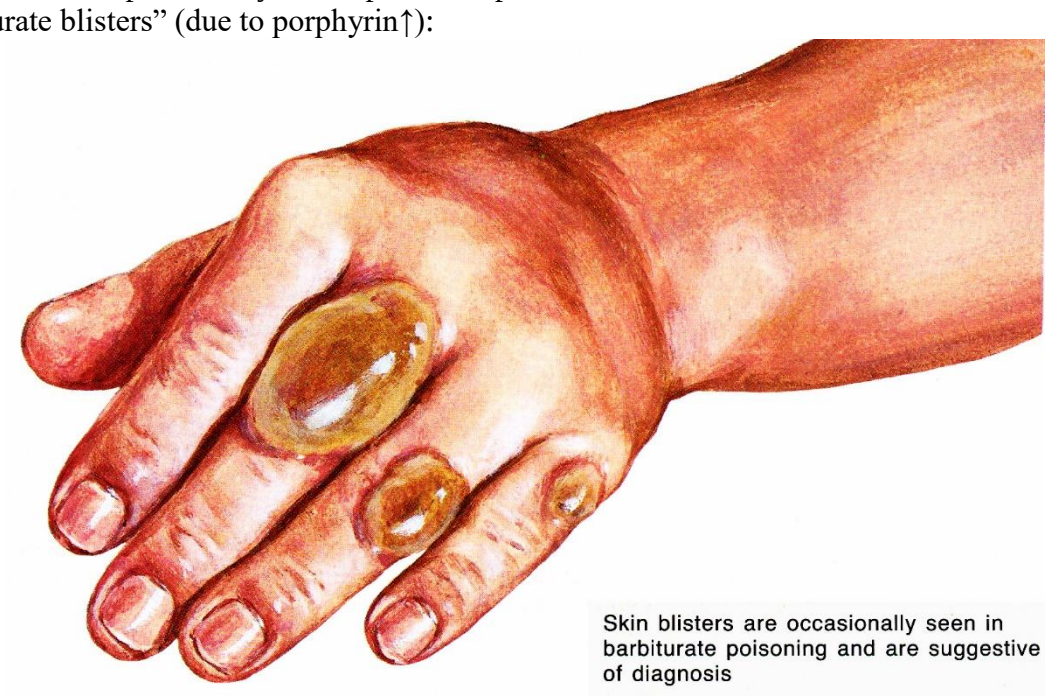
   Withdrawal is much more severe than opiate withdrawal and can result in **DEATH**!!!
4. **P-450 microsomal enzyme induction**:
   1) diminished action of drugs that are dependent on P-450 metabolism (incl. quickly developing **tolerance** to barbiturate itself!!!).
   2) increased porphyrin synthesis (barbiturates are contraindicated in acute intermittent porphyria).
5. **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!!!

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