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*!

1. 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.
  + phenobarbitalhas specific **anti­convulsant activity** different from nonspecific CNS depression. [see p. E3 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)
  + in anesthetic doses, barbiturates significantly **decrease CNS O2 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** (T1/2 –1-2 days) – used as **antiepileptics**.

phenobarbital - duration of action greater than day. [see p. E3 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)

barbital

**short-acting** **barbiturates** (T1/2 –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** (T1/2 –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 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)
       1. status epilepticus in children
       2. eclampsia
       3. young children with recurrent febrile seizures (pheno­barbitalis 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).
  + 1. Producing therapeutic **barbiturate coma** for CNS protection (via reduction of O2 utilization).
    2. **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**!!!

1. **P-450 microsomal enzyme induction**:
2. diminished action of drugs that are dependent on P-450 metabolism (incl. quickly developing **tolerance** to barbiturate itself!!!).
3. increased porphyrin synthesis (barbiturates are contraindicated in acute intermittent porphyria).
4. **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 >>](http://www.neurosurgeryresident.net/Psy.%20Psychiatry\Psy23.%20Substance-related%20Disorders.pdf#Sedatives)
* 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↑):



[Source of picture: Frank H. Netter “Clinical Symposia”; Ciba Pharmaceutical Company; Saunders >>](http://www.amazon.com/gp/product/1933247401)

* 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 >>](http://www.neurosurgeryresident.net/Rx.%20Treatment%20Modalities\Rx.%20Bibliography.pdf)

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