Barbiturates

Last updated: April 21, 2019

MECHANISM OF ACTION

1. At low doses - potentiation of GABA action on CT channel - barbiturates presumably bind to membrane receptors of synaptic sites.
   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 chemoreceptors) up to death.
  • vasomotor medullary center depression occurs only at toxic doses.
  • PENTOBARBITAL has specific anticonvulsant activity different from nonspecific CNS depression. See p. E3 >>
  • in anesthetic doses, barbiturates significantly decrease CNS O2 utilization.

- no analgesic properties (all low doses, even exacerbate pain!), anxiolytic properties much lower than of benzodiazepines!

PHARMACOKINETICS

- absorbed orally.
- distributed widely throughout body; all barbiturates redistribute*: brain → splanchic areas → skeletal muscle → adipose tissue.

- plasma t1/2: 4–5 hours (T1/2 ≈ 30 minutes).

- duration of action 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 >>
  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).
   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).

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 concomitantly 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?).

• 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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