CLINICAL TOXICOLOGY LAB.

5TH STAGE / 1ST SEMESTER

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Clinical Toxicity of Barbiturates

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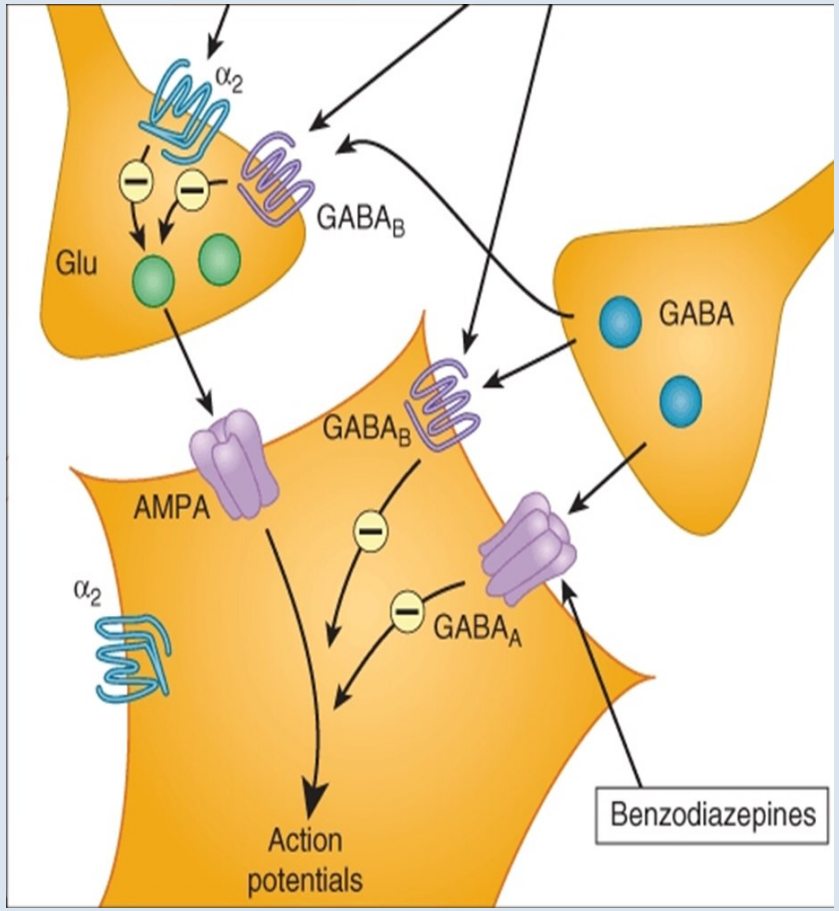
Background & Pharmacology:

- Barbiturates are drugs that act as central nervous system depressants.
- Barbiturates are derivatives of barbituric acid (weak acids)
- Classified according to their duration of action:
  - Long acting (phenobarbital) >>> 12 – 24 hr
  - Intermediate acting (butobarbital) >>> 6 – 12 hr
  - Short acting (pentobarbital, secobarbital) >>> 3- 6 hr
  - Ultrashort acting (thiopental) >>> 15 – 30 min

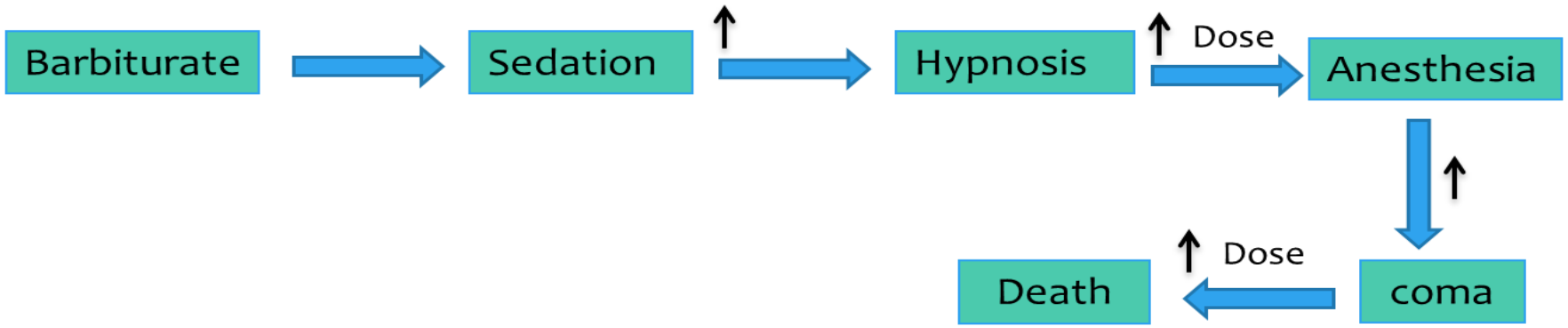
Mechanism of Action:

- Enhance binding of GABA with its receptors, prolonged opening of the Chloride channel (influx of Cl) >>> hyperpolarization
- Block the AMPA receptor, a subtype of glutamate receptor, Leading to decrease the activity of excitatory glutamate neurotransmitter
- At higher concentration, they inhibit the Ca-dependent release of neurotransmitters



Mode of Action & Uses:

- Is a central nervous system (CNS) depressant



- In low doses, used as sedative
- Used as anti-epileptic, for generalized tonic clonic seizures
- Management of status epilepticus
- Pre-anesthetic as sedative, or as induction of anesthesia in certain operations

Disadvantages of using barbiturates:

- They have somewhat low therapeutic index
- High tendency to develop tolerance and dependence (specially with short acting agents)
- High tendency to cause respiratory and cardiovascular depression in high doses
- Inducer of cytochrome P450 (reduce the efficacy of certain drugs, and increase the toxic metabolites for others)
- Additive effect when used with (ethanol, antihistamines, BDZs, opioid analgesics, and other CNS depressants)
- Reduce pain threshold and cause hyperalgesia with high doses
- Used as a hypnotic is obsolete (why?)
- No specific antidote, except for suppurative care

Barbiturate Toxic Effects:

1. Cardiovascular:
   - at the highest doses cause blockade of sympathetic ganglia triggers hypotension , bradycardia, decrease in contractility and cardiac output
   - inhibition of medullary vasomotor centers induce vasodilatation
2. Respiratory Tract:
   - Direct depressant of respiratory center (medulla)
   - Decreased respiratory rate, hypoventilation
   - Cyanosis and shallow respiration
   - non-cardiogenic pulmonary edema
3. CNS:
   - slurred speech, ataxia, lethargy, confusion, headache progressing to anesthesia or coma.

4. Dermal
   - barbiturate blisters, as lesions on fingers, buttocks and near the knees (early stages of toxicity).
5. Metabolic:
   - hypothermia due to depression of thermoregulatory center
6. Gastrointestinal:
   - decreased motility and tune which lead to increases the absorption of the drug
7. Hepatic:
   - cyt-P450 induction, which interact with other drugs that taken and could increased the toxicity of them
8. Renal system:
   - Decreased renal perfusion and GFR

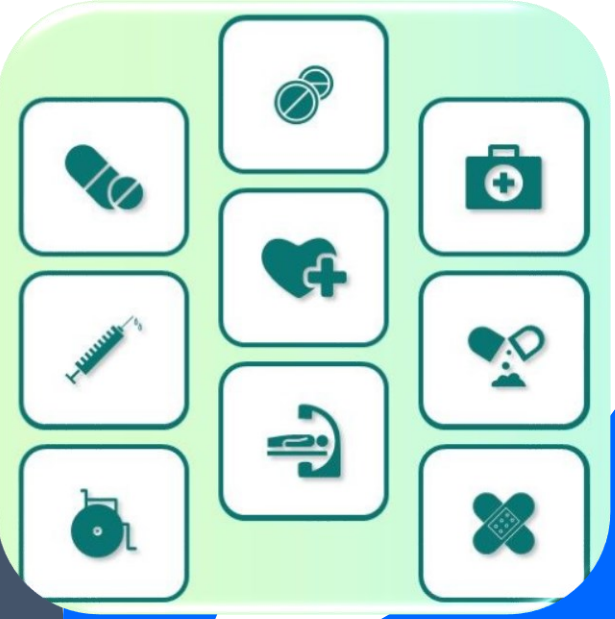
Diagnosis:

- ✓ <u>Clinical and physical signs:</u>
  - Hypothermia (low body temp.)
  - Hypotension (low blood pressure)
  - Nystagmus, mydriasis but responsive to light
  - Hypoventilation and cyanosis
- ✓ <u>Lab. Investigations:</u>
  - CBC
  - Renal function test (Urea, creatinine)
  - Serum electrolytes and pH
  - Serum barbiturates
  - Urine barbiturates analysis (common)

Management:

Aim of treatment/ Treatment of the patient with barbiturate toxicity is predominantly supportive. The mainstay of treatment is the importance of preventing hypoxemia and hypotension

- Management strategies generally fall into 3 major areas:
  - Supportive care
  - Gastrointestinal decontamination
  - Enhancement of elimination



1- Suppurative care:

- **Assess (A) airway and Breathing:**
  - Start oxygen supply
  - Mechanical ventilation if required, specially with signs of respiratory failure
- **Assess (BC) blood volume and circulation:**
  - Fluid replacement to correct hypovolemia
  - Vasopressors to correct hypotension and shock (*high dose of dopamine for shock with ARF, while dobutamine for shock with normal renal function*)
- **Assess (D) level of consciousness:**
  - Usually administer naloxone IV to all patients with altered mental status
  - Measure blood glucose

2- GIT Decontamination:

- **Gastric lavage:**
  - Beneficial in case of barbiturates poisoning even 6 – 12 hr post ingestion (because barbiturates can delay gastric motility)
  - Must be done after protecting the airways

- **Single dose or multidose activated charcoal:**
  - Very effective (because barbiturates are weak acids with high lipid solubility, and delaying gastric motility, thus adsorbed well by charcoal)

3- Enhance Elimination:

Since there is no specific antidote for barbiturates poisoning, the only option to reverse the effects, is by enhance the elimination and maintain suppurative care.

- **Forced diuresis with urine alkalinization:**
  - Alkalinization by the principle of ion trapping
  - Barbiturates are weak acids, unionized in acidic urine with good lipid solubility and tubular reabsorption
  - Barbiturates pKa = 7.2 >>> target urine pH = (8- 8.5) >>> ionization and increased water solubility >>> enhance elimination in urine
  - Sodium bicarbonate (IV) for alkalinization
  - Furosemide or mannitol 10% + KCl (why?)

- **Hemodialysis & hemoperfusion:**
  - Hemoperfusion is much preferred, be of the additional column of activated charcoal
  - Either one of these methods are of great benefits, when the patients is resistant to standard therapeutic measures or present with pulmonary edema, shock, and most importantly renal failure

Thank You For Your Attention

Best of Luck in Everything