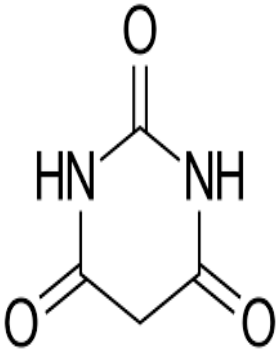
Onset and duration of action of barbiturates

Barbiturate

- Is a drug that acts as a central nervous system depressant. Barbiturates are the derivatives of barbituric acid.



- Barbiturates have addiction potential, both physical and psychological.

- They have largely been replaced by benzodiazepines in routine medical practice, particularly in the treatment of anxiety and insomnia, due to the significant lower risk of overdose and the lack of an antidote for barbiturate overdose.

Mechanism of action

1. Stimulating the inhibitory neurotransmitter system in the brain called(gamma- aminobutyric acid) ((GABA), when barbiturates bind to GABA A_2 recptors lead to prolonged opening of the chloride channel and increase entry of chloride ions in to the nerve cells causes depression of central nervous system.
2. Barbiturates can block excitatory glutamate receptors.
3. Anesthetic concentrations of pentobarbital also block high-frequency sodium channels.

- ***All of these molecular actions lead to decreased neuronal activity.***

Pharmacokinetics

- Barbiturates are well absorbed after oral administration and distribute throughout the body.
- All barbiturates redistribute from the brain to the , to skeletal muscle, and, finally, to adipose tissue
- Barbiturates readily cross the placenta and can depress the fetus.
- These agents are metabolized in the liver, and inactive metabolites are excreted in urine

Therapeutic uses .

- Anesthesia: The ultra–short-acting barbiturates, such as thiopental, have been used intravenously to induce anesthesia
- Anticonvulsant: Phenobarbital has specific anticonvulsant activity. It is used in long-term management of tonic–clonic seizures.

- Sedative/hypnotic: Barbiturates have been used as mild sedatives to relieve anxiety, nervous and tension.
- the use of barbiturates for insomnia is no longer generally accepted, because of their adverse effects and potential for tolerance.
- Butalbital is commonly used in combination products (with acetaminophen and caffeine or aspirin and caffeine) as a sedative to assist in the management of tension-type or migraine headaches.

Pharmacological action

- *On Central Nervous System*

  Depending on the dose barbiturates cause sedation, sleep, anesthesia and coma.

- *On Respiratory system*

  Barbiturates causes the depression of respiratory system.

- *On Cardio-vascular system*

  Barbiturates cause mild decrease in heart rate and blood pressure

- *On Kidney* They reduce blood flow.

On Skeletal muscles

Barbiturates cause decrease the contractions of muscles.

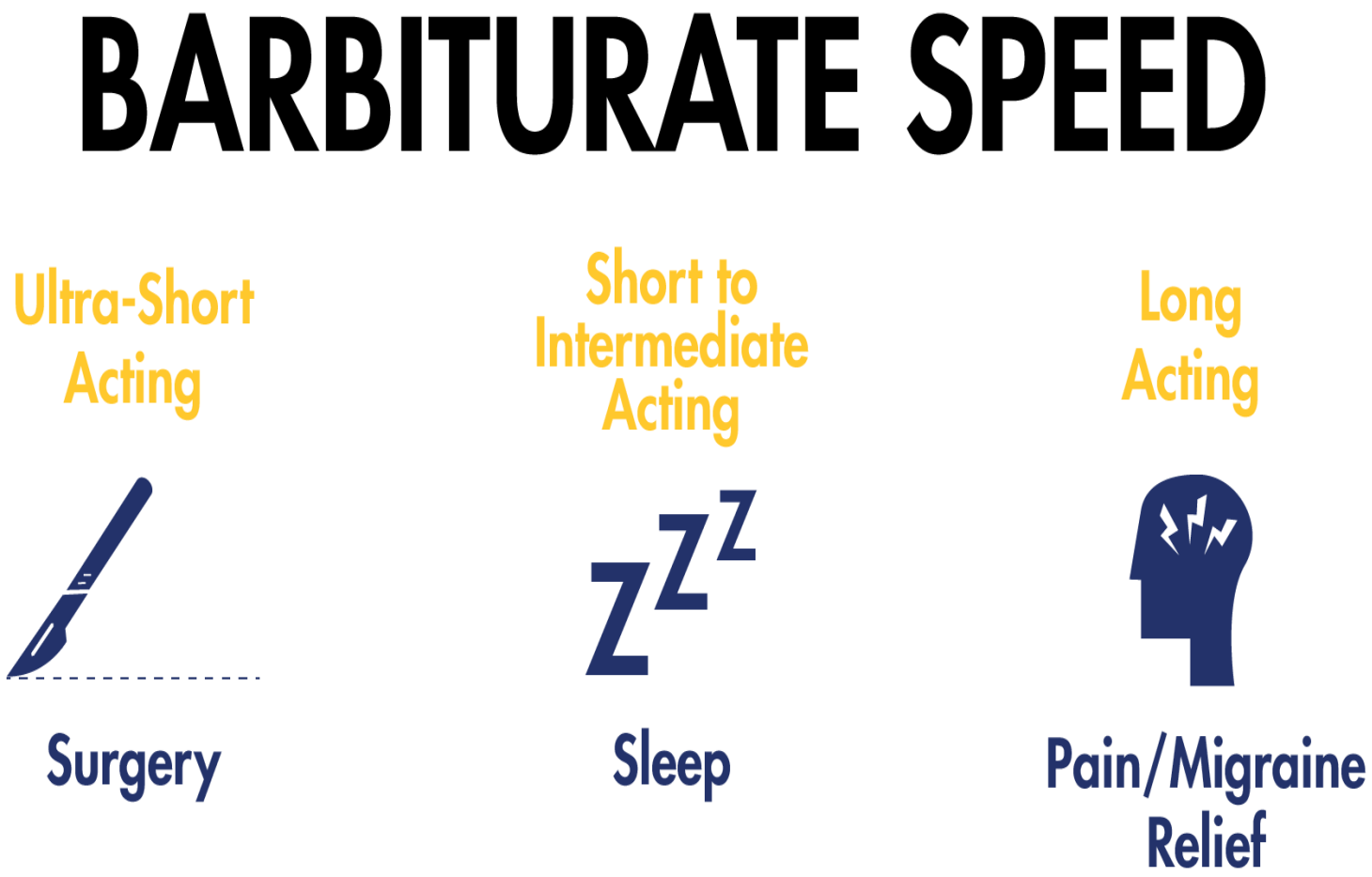
- *On Smooth muscles*

  Barbiturates decrease the tone and motility of smooth muscles in the intestines.

- *On Kidney*

  Barbiturates can decrease the urine output.

Classification of barbiturates



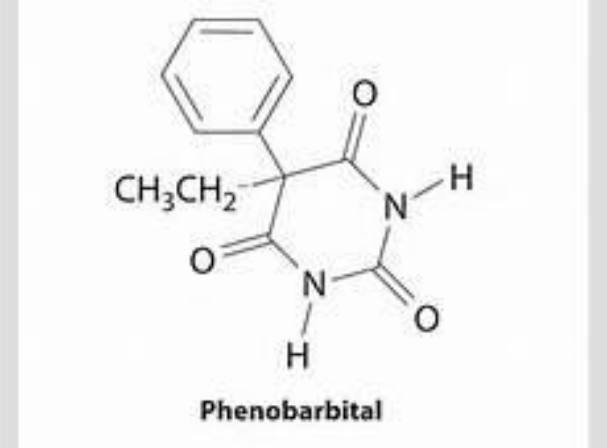
Barbiturates are classified according to their duration of action

- Long-acting barbiturates typically anticonvulsants: relatively slow onset(30-60 minutes) and long duration (10-16hrs)

  ex: Phenobarbital, Mephobarbital

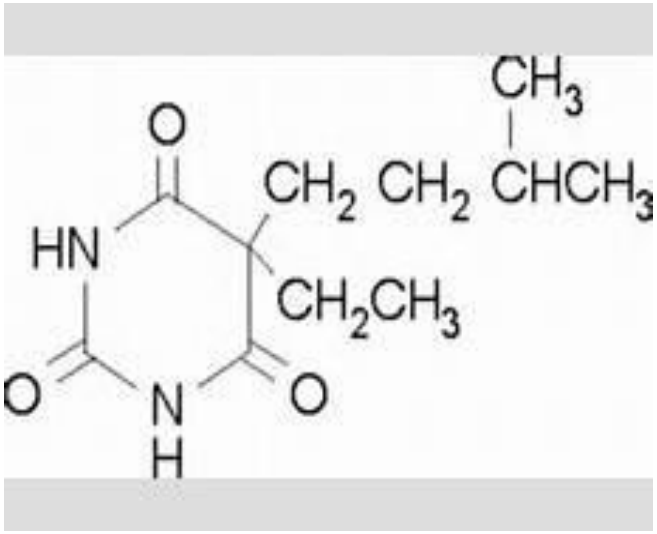
-structure properties: relatively low lipophilicity and low plasma protein binding

Phenobarbital structure

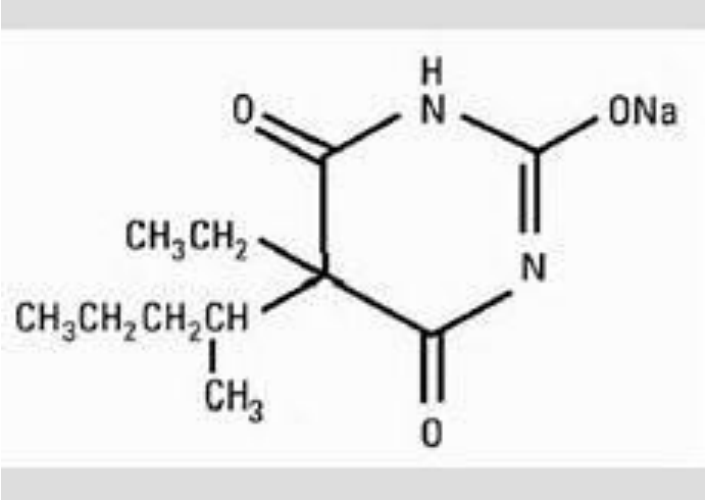


Phenobarbital

- Intermediate acting(sedative/hypnotics): slow onset (45-60 minutes) and intermediate duration (6-8hrs).
- Ex: Talbutal, Amobarbital, Butalbarbita.
- Structure properties: intermediate lipophilicity and intermediate plasma protein binding.
- Amobarbital structure



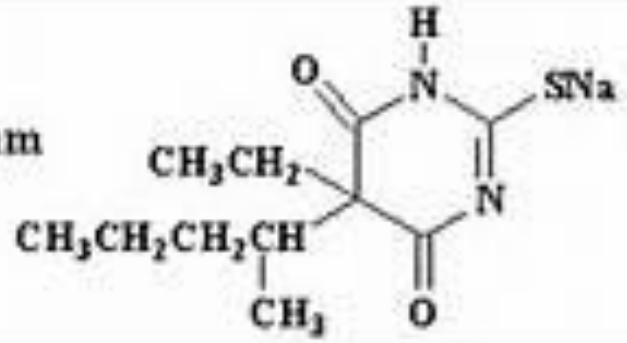
- Short-acting barbiturates(typically sedative/hypnotics) rapid onset (10-15 minutes) and short duration (3-4 hrs)
- : Secobarbital, Pentobarbital
- Structure properties: high lipophilicity and high plasma protein binding, rapid distribution and redistribution.
- Pentobarbital structure



- Ultra–short-acting (induction of anesthesia)
- administered by injection: immediate onset(within seconds) and very short duration (30 minutes).
- Ex: Thiopental
- Structure properties: very high lipophilicity and high plasma protein binding. Rapid distribution and redisrtibution.

Thiopental Sodium

$C_{11}H_{17}N_2NaO_2S$



Onset of action

- Related to rout of administration and lipophlicity. More lipophilic barbiturates are distributed more rapidly to the CNS and thus have more rapid onset.
- Iv administrations have more rapid onset than oral or rectal formulation.

Duration of action (half life)

- Is largely dependent on redistribution. more lipophilic barbiturates undergo more rapid secondary distribution and redistribution to adipose tissue, and thus their action is terminated more rapidlybarbiturates are cleared from plasma by hepatic metabolism and direct renal elimination.

Adverse effects

- Barbiturates cause drowsiness, impaired concentration, mental and physical sluggishness.
- Occasionally, nausea and dizziness occur.
- Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness ,restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death. Death may also result from overdose

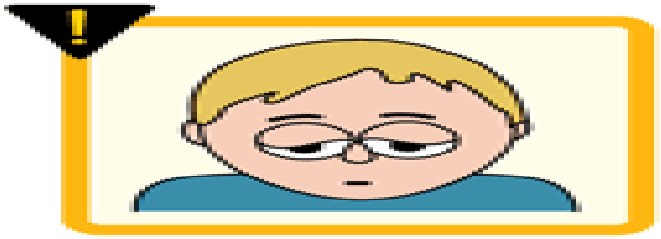
- Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore，Chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system. .

- Potential for addiction
- Drowsiness
- Nausea
- Vertigo

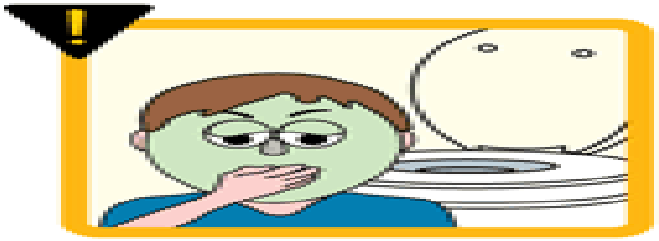
tremor

enzyme induction

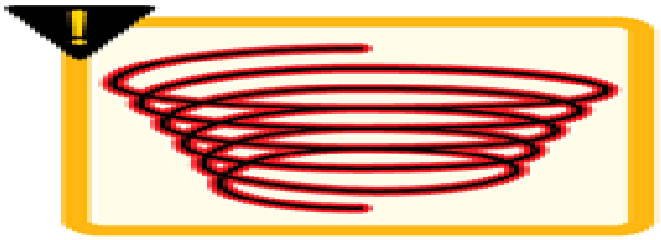
Potential
for addiction



Drowsiness



Nausea



Vertigo

Tremors

Enzyme
induction

CONTRAINDICATIONS

- Phenobarbital is contraindicated in patients who are hypersensitive to barbiturates.
- In patients with a history of manifest or latent porphyria.
- In patients with marked impairment of liver function or respiratory disease in which dyspnea or obstruction is evident.


Thank
you