Sedative Hypnotics

Prepared by:
Anwer Mahmood AL-Jubuori
MSc. Pharmacology and Toxicology
Dept. of Pharmacology
Tikrit university- College of pharmacy
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Introduction

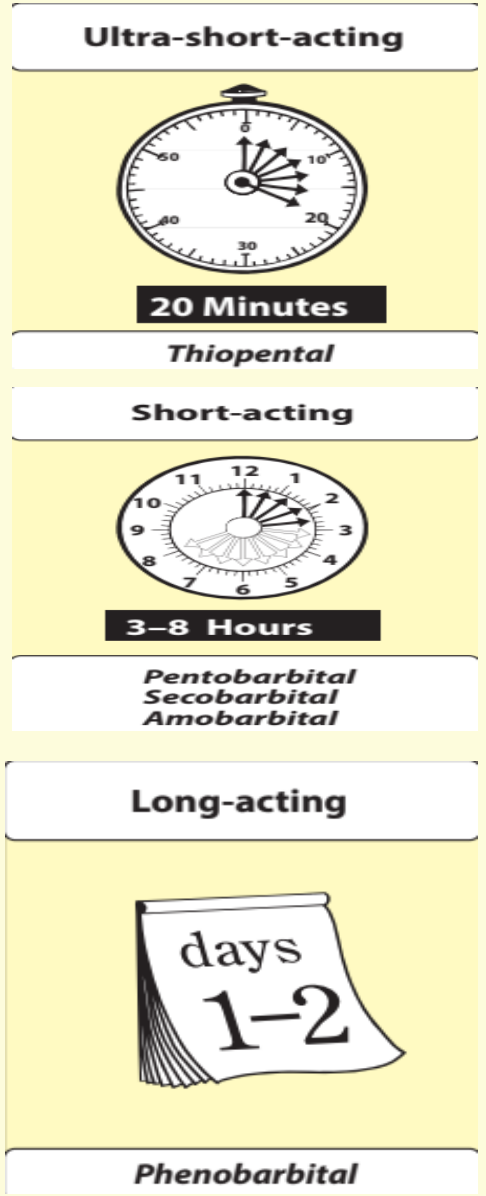
- A **sedative** is defined as a compound that **calms** anxious and restless individuals.
- **Hypnotics** cause drowsiness and facilitate **sleep**, which is close to the normal pattern.
- Sedative – hypnotic group can be **divided** into
- **barbiturate** and **nonbarbiturates** (benzodiazepines, chloral hydrate, meprobamate)
- An **anesthetic** produces deep sleep, **unlike** natural sleep.
- A person who is asleep after a dose of a **hypnotic-sedative** can be **aroused**, but it is **not** possible with anesthesia-induced sleep

Introduction

- Sedative-hypnotic agents are commonly **prescribed** drugs used for a variety of indications including
- the treatment of **restlessness**,
- **Insomnia**
- **Seizures**
- **Alcohol** withdrawal and
- Induction of **anesthesia**.
- Some members of this group are used as **muscle relaxants**,

CLASSIFICATION

- **Ultra-short** acting (duration of action <**15–20** min)
- **Thiopentone**
- **Short-acting** barbiturates have a duration of action of **4** to **6** hr. and include
- **Pentobarbital** and **secobarbital**.
- **Intermediate-acting** barbiturates produce sedation persisting **8** to **10** hr. and include
- **Amobarbital** and **butabarbital**.
- **Long-acting** barbiturates, have a duration of action of **12** to **24** hr. and include
- **Phenobarbital**



Mode of toxicity

- They are common **suicidal** agents.
- **Accidental** over-dosage may occur in **children**.
- Overdose by **dependent** subjects.
- They lead to **automatism** (where the patient repeats the ingestion several times till toxic levels).

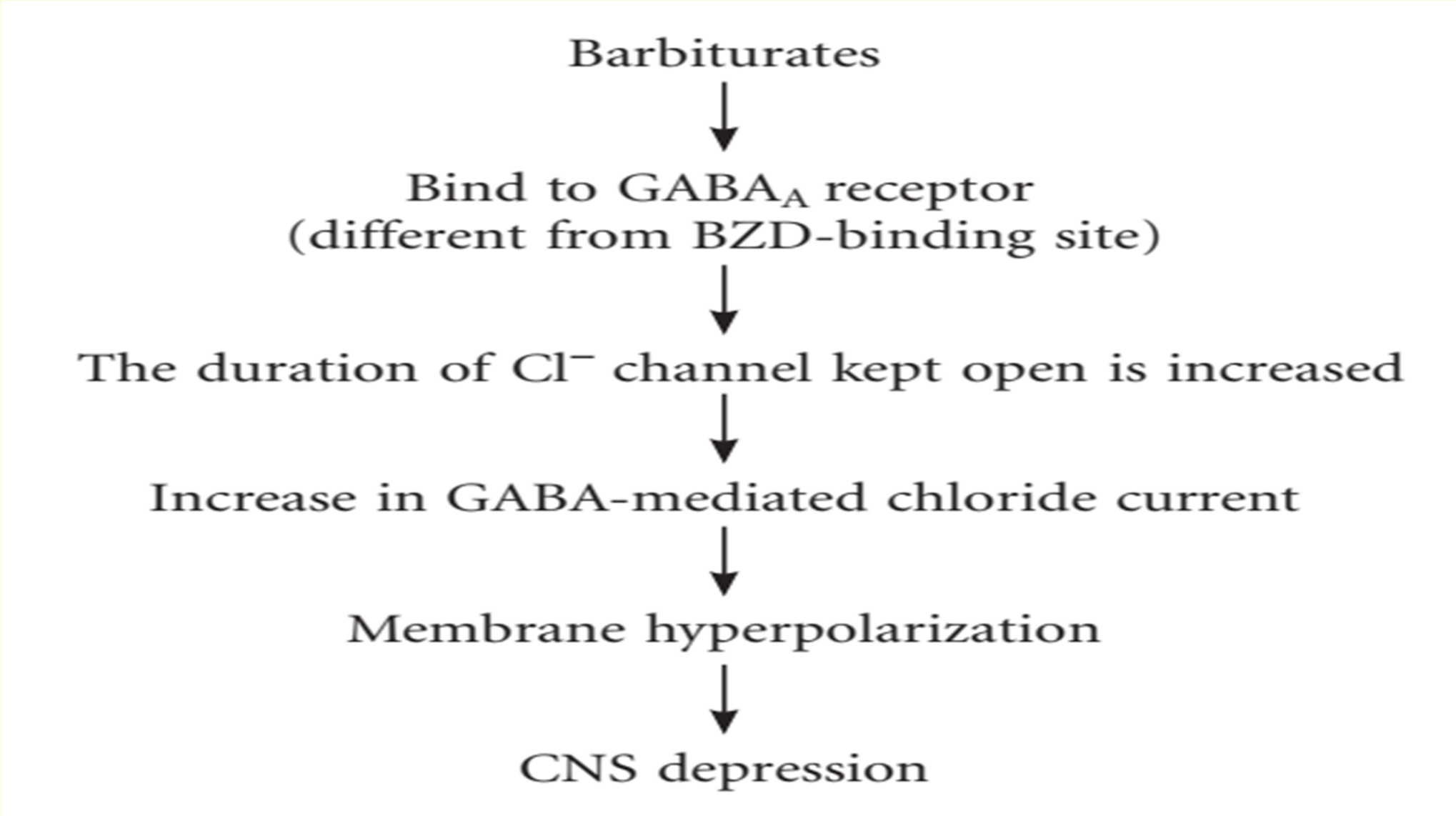
Usual Fatal Dose

- The **toxic dose** of barbiturates **varies**, but an **oral** dose of **one** gram for most barbiturates can cause significant poisoning in an adult.
- **Fatal** cases of ingestion have occurred with doses ranging between **2.0** and **10.0** grams, and the usual **lethal** blood level ranges from **40** to **80** mcg/mL
- Phenobarbitone: **6** to **10** grams.
- Amobarbitone, pentobarbitone, secobarbitone: **2** to **3** grams.

Kinetic

- Most barbiturates administered **orally**. **IV** is usually reserved for management of **status** epilepticus or **induction**/maintenance of general anesthesia.
- Following absorption, barbiturates are **distributed widely**.
- The **long** acting barbiturates have a plasma **half-life** of about **80** hours.
- **Metabolism** of most of these drugs occurs by **oxidation** in the liver resulting in the formation of alcohols, ketones, phenols, or carboxylic acids which are **excreted** in the **urine** as such or in the form of glucuronic acid conjugates.
- Metabolism of barbiturates is more **rapid** in children and is **slower** in the **elderly**.

MOA


Barbiturates
Bind to $GABA_A$ receptor
(different from BZD-binding site)
The duration of Cl^- channel kept open is increased
Increase in GABA-mediated chloride current
Membrane hyperpolarization
CNS depression

Mechanism of toxicity

- The binding site of barbiturates on the **GAB A** receptor is **distinct** from that of the BZD.
- Barbiturates **potentiate** GABA action on **CL entry** into the neuron by **prolonging** the **duration** of the chloride channel openings.
- In addition, barbiturates can **block** excitatory **glutamate** receptors. These molecular actions lead to **decreased** neuronal activity.
- At **high** concentrations, barbiturates have **GABA-mimetic** effect (i.e. barbiturates can directly increase Cl conductance into the neuron).

Mechanism of toxicity

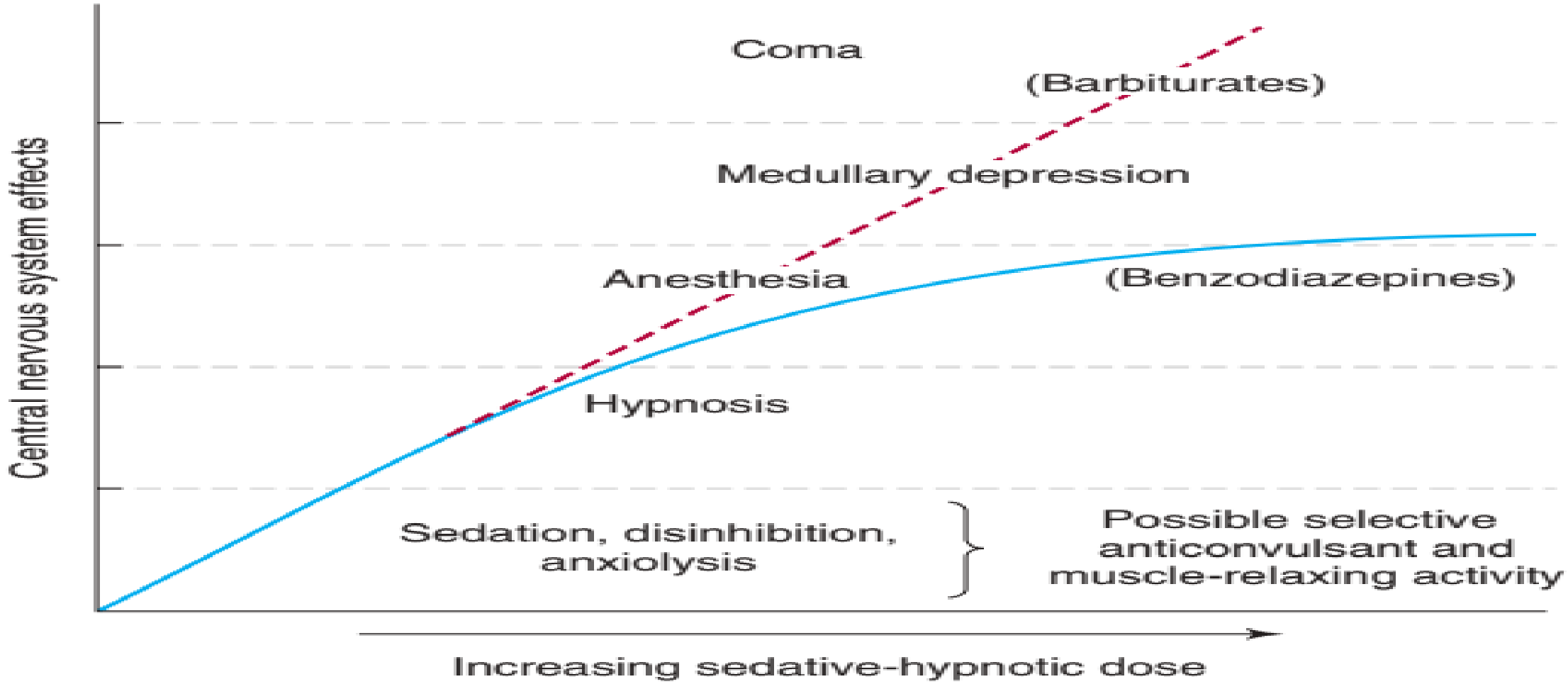


FIGURE 22–2 Relationships between dose of benzodiazepines and barbiturates and their CNS effects.

Clinical picture of acute toxicity

➢**Onset**:

- Very rapid (**15 min**) after short acting barbiturates.
- Delayed (**1-2 h**) after long acting barbiturates.

➢**Manifestations**:

1. **Confusion**
2. **Coma**: It is the **major** sign of acute massive intoxication. Grading of coma is correlated with the blood level of barbiturates.
3. **Respiratory depression**: Results in **hypoventilation** and **apnea** especially with short acting barbiturates. It may be of **very rapid** onset (half an hour) and may cause **death** if the patient is late in reaching hospital.
4. **Hypotension**: severe shock may occur following prolonged **anoxia** or delayed **CPR**.
5. **Hypothermia**.

INVESTIGATIONS

- Arterial blood gases (**ABGs**).
- **Renal** functions.
- **Serum** barbiturate concentrations (phenobarbital) should be **quantified** to determine treatment and its efficacy once initiated (e.g., urinary alkalinization, multi-dose charcoal, and hemodialysis).
- **Urine drug screen** for diagnosis of barbiturate and other drugs.

Treatment of acute barbiturate poisoning

- **Maintain** airway, **breathing** and **circulation**. **Emesis** should be avoided
- Maintain **electrolyte** balance.
- **Gastric lavage** – after stomach wash, administer **activated** charcoal **50** g that may ↑ the elimination of phenobarbitone.
- **Endotracheal intubation** is performed **before** gastric lavage to protect the airway in unconscious patients.
- **Alkaline** diuresis – there is **no** specific antidote for barbiturates; **main treatment** is alkaline diuresis. i.v. $NaHCO_3$ alkalinizes urine. Barbiturates are weakly acidic drugs. In **alkaline urine**, barbiturates exist in **ionized** form, so they are **not** reabsorbed while passing through renal tubules and are rapidly excreted in urine.
- **Hemodialysis** is employed in **severe** cases.

Treatment of acute barbiturate poisoning

❑**Hemodialysis (HD):**

- It is **4 - 6 times** more effective than urinary alkalinization.
- It is of **particular** interest in associated **acute** renal failure.
- However HD is **not useful** in **short** acting Barbiturates.

❑**Hemofiltration**:

- Is **more effective** than HD and is **recommended** in patients with **heart failure** with or without pulmonary edema or **renal** insufficiency.


THANK YOU