YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 1 (Part 2) - Pharmacology

Lec. Title : Anxiolytic & Hypnotic Drugs (Sedative Hypnotics)

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Part 2

Anxiolytic and Hypnotic Drugs

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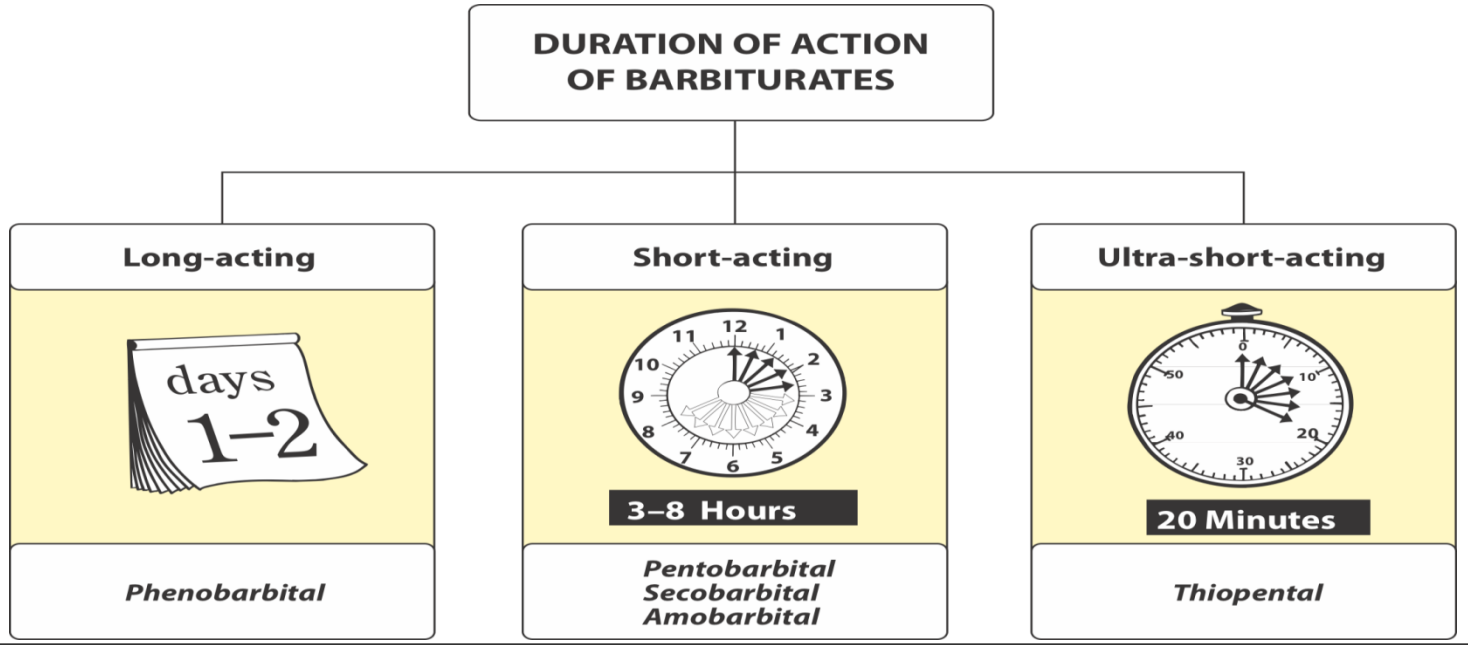
Objectives

1. Identify the major chemical classes of sedative-hypnotics.
2. Describe the pharmacodynamics of benzodiazepines, including interactions with neuronal membrane receptors.
3. Compare the pharmacokinetics of commonly used benzodiazepines and barbiturates and discuss how differences among them affect clinical use.
4. Describe the clinical uses of sedative-hypotics.
5. Describe the common adverse effects and drug interaction of sedative-hynotics
6. Understand tolerance and dependence induced by sedative-hypnotics.
7. Understand the therapeutic indications and adverse effects of benzodiazepines antagonists

Barbiturates

- Largely replaced by benzodiazepines because they:
- Induce tolerance
- Induce drug-metabolising enzymes
- Cause physical dependence
- Associated with withdrawal symptoms
- Narrower therapeutic window compared to benzodiazepines



Barbiturates

- MOA: decreased neural activity
- Main sedative and hypnotic effect: by binding to $GABA_A$ receptors (at a different site than benzodiazepine interaction site) – potentiate GABA action by prolonging the duration of the chloride channel opening

- Furthermore, by blocking the excitatory glutamate receptors

- Anaesthetic effect: by blocking the high-frequency Na-channels

Sheet # 1

BARBITURATES:

We do not use barbiturates for anxiety due to their many side effects. Its CNS depression is worse than benzodiazepines due to it working directly and indirectly. It increases the duration of opening of channels.

Benzodiazepines are more effective than barbiturates due to barbiturates having very high tolerance. That tolerance happens when CNS cells lose their receptors for them. Moreover, there is kinetic tolerance when they induce liver enzymes to break them down (interaction with other drugs and enzymes).

The action of the barbiturates is more and stronger but because the tolerance it have less effect.

The action of barbiturates is more but the effect of benzodiazepines is more.

Barbiturates

Action and Mechanism	Therapeutic Use	Drugs
Depression of CNS: -Low dose: sedation -Higher dose: hypnosis -Highest dose: anaesthesia -Toxic dose: coma and death	Anaesthesia	Ultra-short-acting: Thiopental (I.V)- replaced by other agents
	Anticonvulsant	Long-acting: Phenobarbital
	Sedative and hypnotic	Short-acting: Secobarbital and Amobarbital – no longer recommended

Sheet # 2

Phenobarbital: given as anti-epileptic.

All other barbiturates are not in use anymore.

Flumazenil is not a barbiturates antagonist because barbiturates' receptors are not the same ones for benzodiazepines. It only works for benzodiazepines.

Barbiturates close sodium channels. They open chloride channels leading to hyperpolarization. All this leads to CNS depression.

Thiopental is ultra-short acting and is used for anesthetic purposes for short durations.

What causes thiopental's ultra-short acting? Redistribution not metabolism. Metabolism leads to elimination but only redistribution can stop the drug action.

Barbiturates have a narrow therapeutic index meaning the difference between low dose (sedation), higher dose (hypnosis), highest dose (anesthesia) and toxic dose (death) is very small. It takes a very small increasing in dosage to get to the next level, making them dangerous.

Barbiturates

- PK properties:

- Redistribute widely throughout the body:

  Brain → splanchnic areas → skeletal muscles → adipose tissues

- Readily cross the placenta → fetus depression

- Barbiturates induce liver CYP450 enzymes

- Metabolized in liver and excreted in urine

Sheet # 3

It can cross the placenta due to its lipophilic nature. They should be avoided during pregnancy.

Metabolized in liver and excreted in urine.

Barbiturates

- Adverse effects:

- *CNS*: drowsiness, impaired concentration, mental and physical sluggishness. Synergism with *ethanol*
- *Drug hangover*: feeling of tiredness after waking-up from a hypnotic dose of barbiturates
- *Respiratory depression* (toxicity): due to suppression of the hypoxic and chemoreceptor response to CO_2

Sheet # 4

Drug hangover refers to "the effect of the drug is beginning to disappear".

Barbiturates cause the respiratory system to stop detecting Co2 by suppressing chemoreceptor response to Co2. This leads to respiratory depression.

Barbiturates

- Physical dependence:

  Abrupt withdrawal: tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium and cardiac arrest. It can result in death

- Poisoning:

- Respiratory depression
- Central cardiovascular depression
- Treatment: **no specific antidote.**
- **Artificial respiration** and stomach purging would help

Sheet # 5

Physical dependence of barbiturates leads to withdrawal. This means patients suffer from symptoms the exact opposite of what the drugs used to induce.

There is no antidote for barbiturates. You can only treat the symptoms (symptomatic treatment).

OTHER HYPNOTIC AGENTS

Zolpidem

- *acts on benzodiazepine receptors (BZ 1) & facilitate GABA mediated neuronal inhibition.*
- *Its action is antagonized by flumazenil.*
- *No anticonvulsant or muscle-relaxing properties.*

ZOLPIDEM:
Non benzodiazepine BUT acts on benzodiazepine receptors. It is only a short acting HYPNOTIC drug.

- *Few withdrawal effects*
- *Minimal rebound insomnia*
- *Little or no tolerance occurs with prolonged use*
- *Short duration of action.*

Note:

- *The nonbenzodiazepine drugs, zolpidem, zaleplon, and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics.*

Sheet # 6

ZALEPLON, EAZOPICLONE and ZOLPIDEM maintain natural sleep stages. They do not alter the sleep stages. Zolpidem only effects the sleep latency (entrance into sleep).

Antihistamines have anxiolytic effects, but they are less used due to their anticholinergic effects.

RAMELTEON:

Hypnotic drug that does not disturb natural sleep stages. It perfectly imitates melatonin.

Antihistamines

- *as diphenhydramine, hydroxyzine and doxylamine,*
- *are effective in treating mild types of insomnia.*
- *Have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines.*