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MEDICINAL CHEMISTRY – I

UNIT 5

TOPIC :

- **Drugs acting on Central Nervous System**
  General anesthetics :
  Inhalation anesthetics : Halothane, Methoxyflurane, Enflurane, Sevoflurane, Isoflurane, Desflurane.
  Ultra short acting barbitutrates : Methohexital sodium, Thiamylal sodium, Thiopental sodium.
  Dissociative anesthetics : Ketamine hydrochloride.*

General Anesthetics

- **General anesthetics** are drugs used during surgery to induce **complete loss of consciousness**, **analgesia**, **amnesia**, and **immobility**.
- They act on the **entire CNS** to depress neuronal activity.
- The patient **does not perceive pain** and remains unconscious throughout the procedure.

Mechanism of Action (General Principles)

General anesthetics produce their effects through **multiple mechanisms** on the CNS:

1. Enhancement of Inhibitory Pathways

- Most anesthetics enhance GABA-A receptor activity.
- Leads to hyperpolarization of neurons, reduced neuronal excitability → sedation, amnesia, unconsciousness.

2. Inhibition of Excitatory Pathways

- Some anesthetics inhibit excitatory neurotransmitters such as glutamate, especially at NMDA receptors.
- Example: Ketamine blocks NMDA receptors →produces dissociative anesthesia.

3. Modulation of Ion Channels

- Potassium (K^+) channels: promote K^+ efflux →hyperpolarization → reduced excitability.
- Sodium (Na^+) channels: inhibition →reduced generation of action potentials.

Classification of General Anesthetics

1. Inhalation Anesthetics

- Halothane
- Methoxyflurane
- Enflurane
- Sevoflurane
- Isoflurane
- Desflurane

2. Ultra Short-Acting Barbiturates

- Thiopental sodium
- Methohexital
- Thiamylal sodium

3. Dissociative Anesthetics

- Ketamine hydrochloride

Inhalation Anesthetics

- Inhalation anesthetics are **gaseous or volatile liquid agents** administered through inhalation with oxygen.
- They induce **general anesthesia** by **depressing the CNS**, producing **unconsciousness, amnesia, analgesia, and immobility**.
- The anesthetic effect depends on **rapid absorption into the blood and brain** at sufficient concentration.

Mechanism of Action

1. **Enhancement of Inhibitory Neurotransmission**
    - Most inhalation anesthetics **enhance GABA-A receptor activity**, increasing **Cl^- influx**.
    - Hyperpolarization → reduced neuronal excitability → sedation, amnesia, and unconsciousness.
2. **Activation of Glycine Receptors**
    - Some agents (e.g., **isoflurane**) activate **glycine receptors** in the spinal cord → enhance inhibitory transmission → muscle relaxation.
3. **Inhibition of Excitatory Neurotransmission**
    - Inhibit **glutamate activity**, particularly at **NMDA receptors**.
    - Notably, **nitrous oxide** and **xenon** act primarily via NMDA receptor blockade → reduce neuronal excitation.
4. **Ion Channel Modulation**
    - May influence **K^+ and Na^+ channels** → stabilize neuronal membranes and reduce action potential generation.

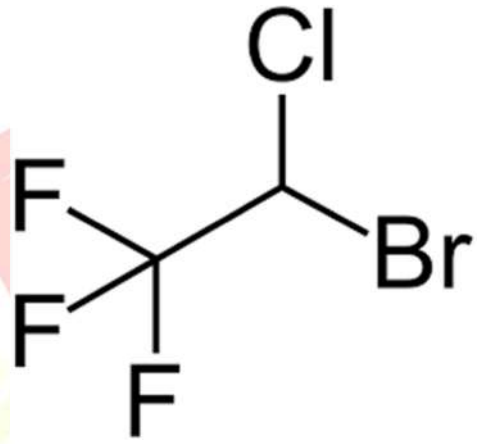
Examples

- **Halothane**
- **Methoxyflurane**
- **Enflurane**
- **Sevoflurane**
- **Isoflurane**
- **Desflurane**

Halothane

Structure

- Chemical class: Volatile halogenated hydrocarbon anesthetic.
- Chemical formula: $C_2HBrClF_3$ (2-bromo-2-chloro-1,1,1-trifluoroethane).
- Physical properties: Colorless, non-flammable liquid with a sweet smell; volatile and highly lipophilic.



Mechanism of Action (MOA)

- Central nervous system depression:
  - Enhances GABA-A receptor activity, increasing chloride influx → hyperpolarization of neurons → CNS depression.
- Inhibits excitatory neurotransmission:
  - Inhibits NMDA (glutamate) receptors → reduces neuronal excitation.
- Effects on ion channels:
  - Modulates potassium (K^+) channels → hyperpolarization
  - Inhibits sodium (Na^+) channels → reduced action potential generation.
- Net effect → unconsciousness, analgesia, amnesia, and muscle relaxation.

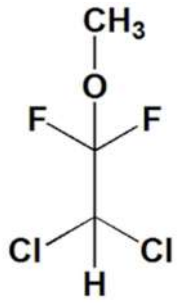
Therapeutic Uses

- General anesthesia:
  - Induction and maintenance of surgical anesthesia (rarely used now due to side effects).
- Adjunct in combination with other anesthetics for balanced anesthesia.

Methoxyflurane

Structure

- Chemical class: Volatile halogenated ether anesthetic.
- Chemical formula: $C_3H_4Cl_2F_2O$ (2,2-dichloro-1,1-difluoroethyl methyl ether).
- Physical properties: Colorless liquid with a sweet, pleasant odor; highly lipophilic and volatile.



methoxyflurane

Mechanism of Action (MOA)

- CNS depression:
  - Enhances GABA-A receptor activity, increasing chloride influx → hyperpolarization → decreased neuronal excitability.
- Inhibition of excitatory pathways:
  - Blocks NMDA glutamate receptors, reducing excitatory synaptic transmission.
- Effects on ion channels:
  - Modulates K^+ channels → hyperpolarization
  - Inhibits Na^+ channels → reduces action potential generation.
- Net result → unconsciousness, analgesia, and muscle relaxation during anesthesia.

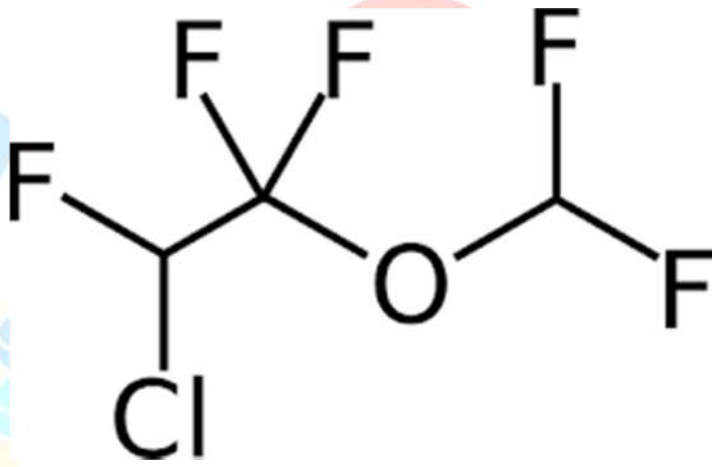
Therapeutic Uses

- General anesthesia:
  - Historically used for surgical anesthesia, but largely replaced due to nephrotoxicity concerns.
- Occasionally used in low doses for analgesia in trauma or minor procedures.

Enflurane

Structure

- Chemical class: Volatile halogenated ether anesthetic.
- Chemical formula: $C_3H_2ClF_5O$ (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether).
- Physical properties: Colorless, sweet-smelling liquid; volatile and moderately lipophilic.



Mechanism of Action (MOA)

- CNS depression:
  - Enhances GABA-A receptor activity, increasing chloride influx → hyperpolarization → reduced neuronal excitability.
- Inhibition of excitatory pathways:
  - Blocks NMDA glutamate receptors, decreasing excitatory neurotransmission.
- Ion channel modulation:
  - Activates potassium channels → hyperpolarization
  - Inhibits sodium channels → reduced action potential generation.
- Net result → unconsciousness, analgesia, and immobility during anesthesia.

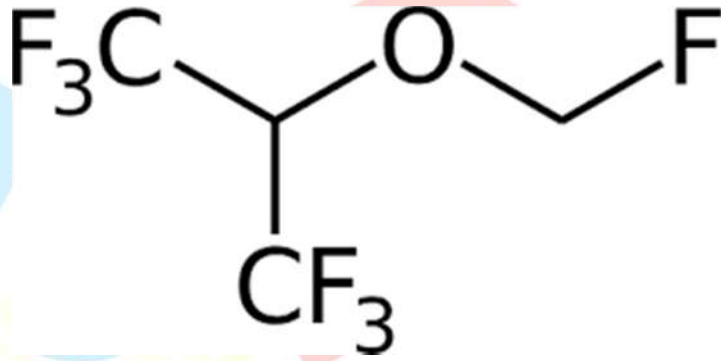
Therapeutic Uses

- General anesthesia for surgical procedures.
- Provides moderate muscle relaxation and rapid induction and recovery.

Sevoflurane

Structure

- Chemical class: Volatile halogenated ether anesthetic.
- Chemical formula: $C_4H_3F_7O$ (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether).
- Physical properties: Colorless, non-pungent liquid; sweet odor; highly volatile and lipophilic.



Mechanism of Action (MOA)

- Enhancement of inhibitory pathways:
  - Potentiates GABA-A receptor activity → increased Cl^- influx → neuronal hyperpolarization → CNS depression.
- Inhibition of excitatory pathways:
  - Blocks NMDA glutamate receptors, reducing excitatory neurotransmission.
- Ion channel modulation:
  - Activates potassium channels → hyperpolarization
  - Inhibits sodium channels → reduces action potential firing.
- Net effect → rapid induction of anesthesia, analgesia, and muscle relaxation.

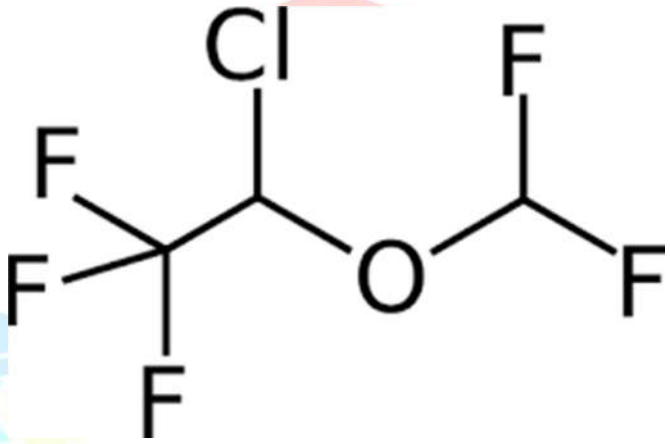
Therapeutic Uses

- Induction and maintenance of general anesthesia for surgeries.
- Preferred in pediatric anesthesia due to non-pungent odor → smooth induction.
- Rapid onset and recovery suitable for outpatient procedures.

Isoflurane

Structure

- Chemical class: Volatile halogenated ether anesthetic.
- Chemical formula: $C_3H_2ClF_5O$ (2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane).
- Physical properties: Colorless, non-flammable liquid; pungent odor; highly lipophilic and volatile.



Mechanism of Action (MOA)

- Enhancement of inhibitory pathways:
  - Potentiates GABA-A receptors → increased chloride influx → hyperpolarization → CNS depression.
- Inhibition of excitatory pathways:
  - Blocks NMDA (N-methyl-D-aspartate) glutamate receptors, reducing excitatory neurotransmission.
- Ion channel modulation:
  - Activates potassium channels → hyperpolarization
  - Inhibits sodium channels → reduces action potential propagation.
- Net effect → induction and maintenance of anesthesia, analgesia, and immobility.

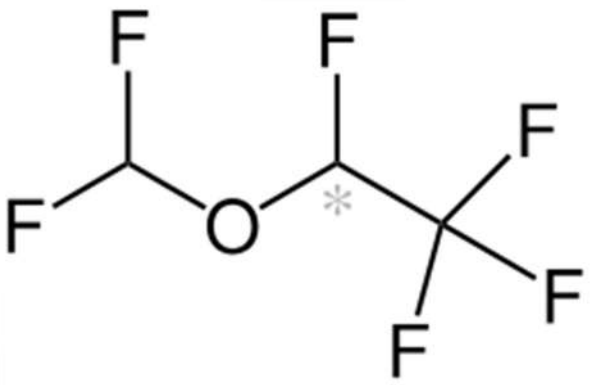
Therapeutic Uses

- Maintenance of general anesthesia for surgeries.
- Preferred in patients with cardiovascular stability needs.
- Suitable for long-duration procedures due to good muscle relaxation and controlled depth of anesthesia.

Desflurane

Structure

- Chemical class: Volatile halogenated ether anesthetic.
- Chemical formula: $C_3H_2F_6O$ (2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane).
- Physical properties: Colorless, low-boiling liquid; pungent odor; highly volatile and lipophilic.



Mechanism of Action (MOA)

- Enhancement of inhibitory neurotransmission:
  - Potentiates GABA-A receptors → increased chloride influx → neuronal hyperpolarization → CNS depression.
- Inhibition of excitatory neurotransmission:
  - Blocks NMDA glutamate receptors, reducing excitatory signaling.
- Ion channel modulation:
  - Activates potassium channels → hyperpolarization
  - Inhibits sodium channels → reduced neuronal firing.
- Net effect → rapid induction and maintenance of general anesthesia, analgesia, and immobility.

Therapeutic Uses

- Maintenance of general anesthesia, especially in outpatient or short surgical procedures.
- Rapid induction and recovery due to low blood-gas partition coefficient.
- Suitable for patients requiring precise control of anesthetic depth.

Ultra Short-Acting Barbiturates

- Ultra short-acting barbiturates are **intravenous anesthetic agents** used for **rapid induction of anesthesia**.
- They produce **quick unconsciousness** suitable for **surgical procedures** and as **pre-anesthetic agents**.
- Duration of action is short due to **rapid redistribution from the brain to peripheral tissues**.

Mechanism of Action (MOA)

- Act primarily by **enhancing GABA-A receptor activity** in the CNS.
- **Mechanism steps:**
    1. Bind to **GABA-A receptor** at a site distinct from benzodiazepines.
    2. **Increase the duration** of chloride (Cl^-) channel opening when GABA is present.
    3. **Chloride influx → neuronal hyperpolarization → decreased excitability.**
- Net effect: **rapid CNS depression → unconsciousness**.

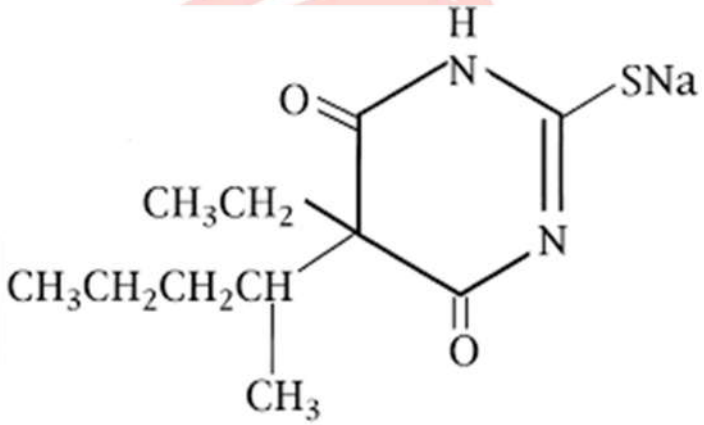
Examples

- **Thiopental sodium**
- **Methohexital sodium**
- **Thiamylal sodium**

Thiopental Sodium

Structure

- Chemical class: Ultra-short-acting barbiturate (barbituric acid derivative).
- Chemical formula: $C_{11}H_{18}N_2O_3SNa$.
- Physical properties: White to slightly yellow crystalline powder; soluble in water (as sodium salt); administered intravenously.



Mechanism of Action (MOA)

- GABA-A receptor potentiation:
  - Binds to barbiturate site on GABA-A receptors → prolongs chloride channel opening → neuronal hyperpolarization → CNS depression.
- Direct effect at high doses:
  - Can directly open chloride channels independent of GABA.
- Net effect:
  - Rapid induction of general anesthesia, sedation, and respiratory depression.

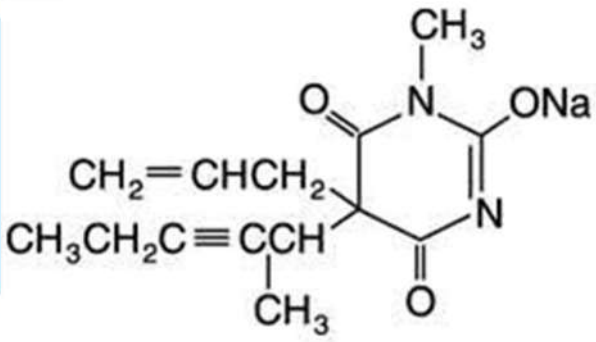
Therapeutic Uses

- Induction of general anesthesia (ultra-short acting for rapid onset).
- Adjunct to anesthesia in short surgical procedures.
- Occasional use in medically-induced coma for refractory status epilepticus or intracranial pressure control (rare).

Methohexital Sodium

Structure

- Chemical class: Ultra-short-acting barbiturate (barbituric acid derivative).
- Chemical formula: $C_{12}H_{18}N_2O_3Na$.
- Physical properties: White crystalline powder; highly soluble in water; administered intravenously.



Mechanism of Action (MOA)

- GABA-A receptor potentiation:
  - Binds to barbiturate site on GABA-A receptors, prolonging chloride channel opening → hyperpolarization → CNS depression.
- Direct effect at higher concentrations:
  - Can directly open chloride channels independent of GABA.
- Net effect:
  - Rapid induction of anesthesia, sedation, and reduced neuronal excitability.

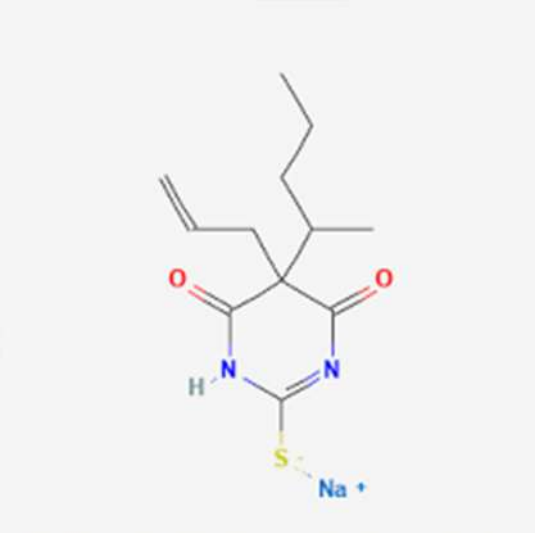
Therapeutic Uses

- Induction of general anesthesia for short surgical procedures.
- Sedation in minor surgeries or diagnostic procedures requiring quick recovery.

Thiamylal Sodium

Structure

- Chemical class: Ultra-short-acting barbiturate (barbituric acid derivative).
- Chemical formula: $C_{12}H_{16}N_2O_3SNa$.
- Physical properties: White crystalline powder; highly water-soluble; administered intravenously.



Mechanism of Action (MOA)

- GABA-A receptor potentiation:
  - Binds to the barbiturate site on GABA-A receptors, prolonging chloride ion channel opening → hyperpolarization → CNS depression.
- Direct effect at higher doses:
  - Can open chloride channels independently of GABA.
- Net effect:
  - Rapid induction of anesthesia with short duration; CNS depression.

Therapeutic Uses

- Induction of general anesthesia for short surgical procedures.
- Sedation for minor surgical or diagnostic procedures.

Dissociative Anesthetics

- Dissociative anesthetics are a **class of drugs that produce anesthesia by dissociating the **cerebral cortex from the limbic system**.
- The patient may appear **awake but is analgesic, amnesic, and immobile**.
- They are **primarily used in short surgical procedures**, trauma care, and pediatric anesthesia.

Mechanism of Action (MOA)

1. **NMDA Receptor Antagonism:**
    - Blocks **N-methyl-D-aspartate (NMDA) receptors** → inhibits excitatory glutamate neurotransmission.
    - Reduces neuronal excitation → analgesia and unconsciousness.
2. **Additional Effects:**
    - Activates **opioid receptors** → contributes to analgesia.
    - Modulates **catecholamine release** → increases heart rate and blood pressure (unlike most other anesthetics).

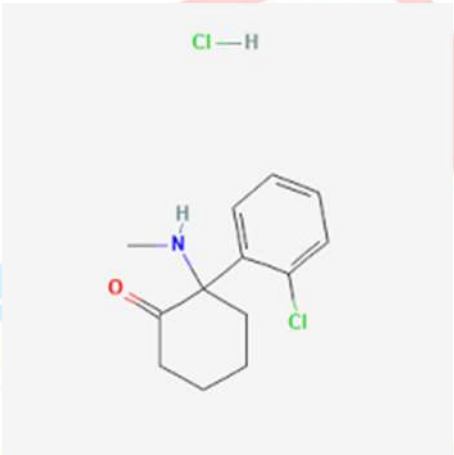
Examples

- Ketamine hydrochloride

Ketamine Hydrochloride

Structure

- **Chemical class:** Dissociative anesthetic; phencyclidine (PCP) derivative.
- **Chemical formula:** $C_{13}H_{16}ClNO$.
- **Physical properties:** White crystalline powder; water-soluble; usually administered intravenously or intramuscularly.



Mechanism of Action (MOA)

- **NMDA receptor antagonism:**
  - Blocks **N-methyl-D-aspartate (NMDA) glutamate receptors** in the CNS → prevents excitatory neurotransmission → dissociative anesthesia.
- **Other effects:**
  - Partial agonist at opioid receptors → mild analgesia.
  - Modulates monoaminergic and cholinergic pathways → contributes to amnesia and sedation.
- **Net effect:**
  - Produces **dissociative anesthesia**: analgesia, amnesia, and catalepsy, while preserving some airway reflexes and cardiovascular function.

Therapeutic Uses

- **Induction and maintenance of anesthesia** (especially in short procedures).
- **Analgesia** for burn dressing, minor surgery, or emergency procedures.