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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 barbiturates :** 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

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## 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<sup>-</sup> 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<sup>+</sup> and Na<sup>+</sup> channels** → stabilize neuronal membranes and reduce action potential generation.

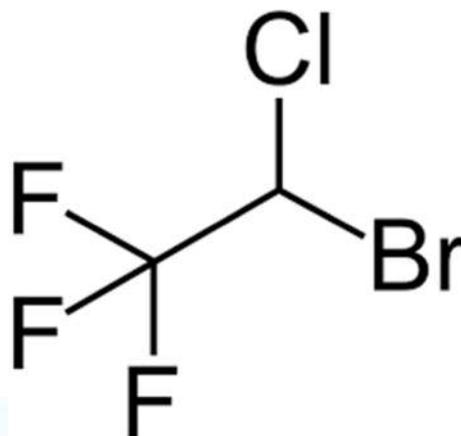
### Examples

- **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.

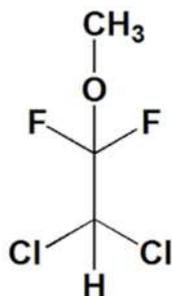
### Therapeutic Uses

- 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.



### 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.

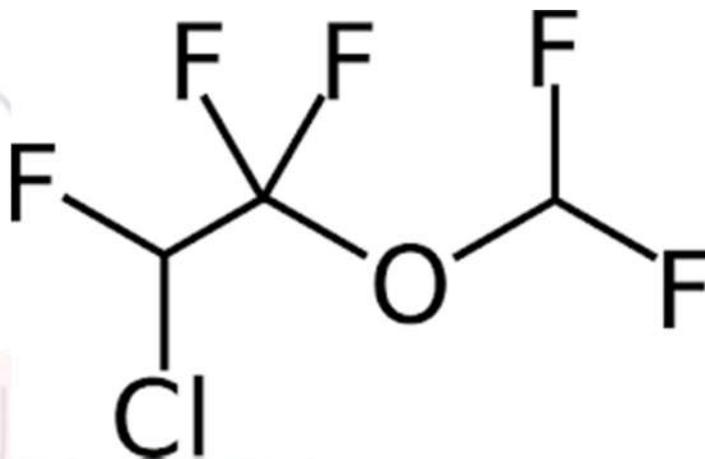
### Therapeutic Uses

- 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.

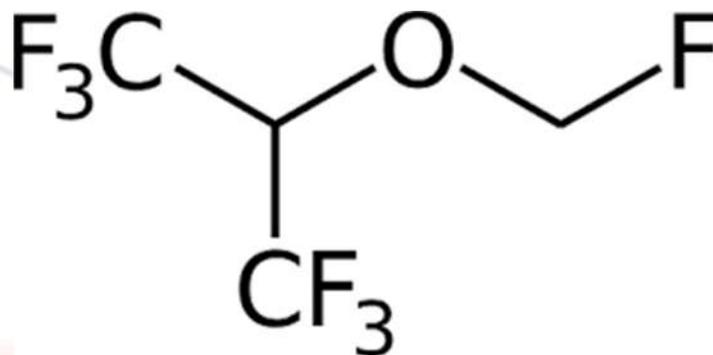
### Therapeutic Uses

- 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.

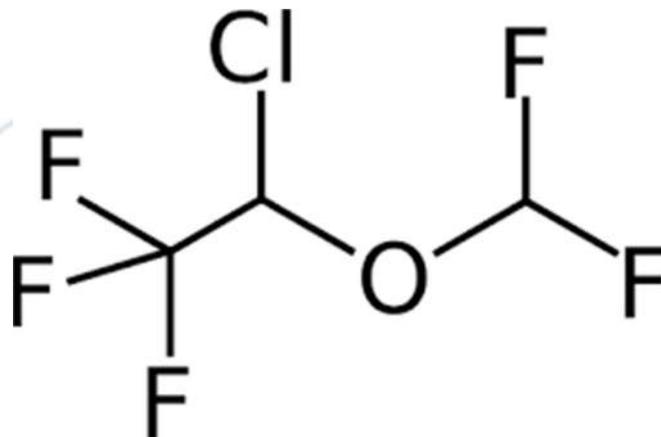
### Therapeutic Uses

- 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.

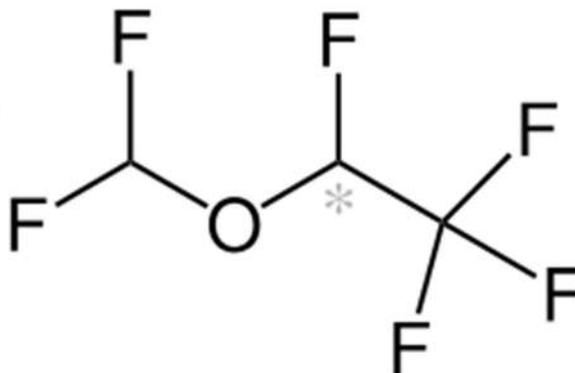
### Therapeutic Uses

- 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 ( $\text{Cl}^-$ ) channel opening when GABA is present.
  3. Chloride influx  $\rightarrow$  neuronal hyperpolarization  $\rightarrow$  decreased excitability.
- Net effect: rapid CNS depression  $\rightarrow$  unconsciousness.

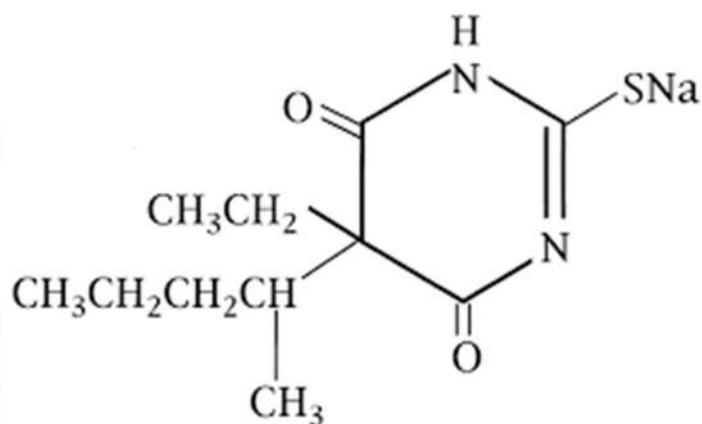
### Examples

- 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.

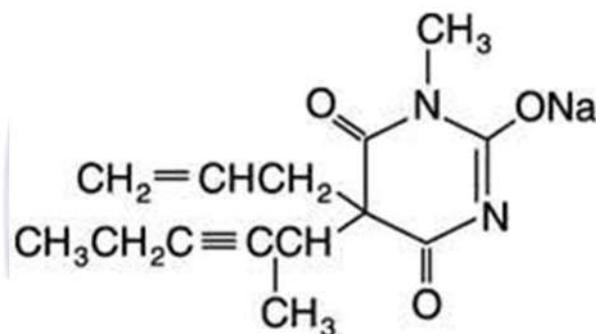
### Therapeutic Uses

- 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.

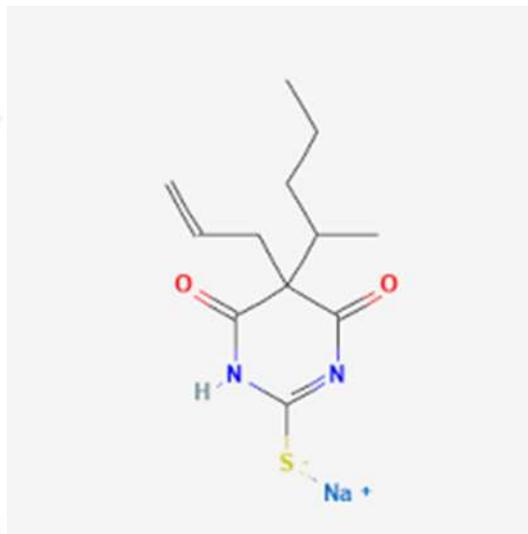
### Therapeutic Uses

- 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

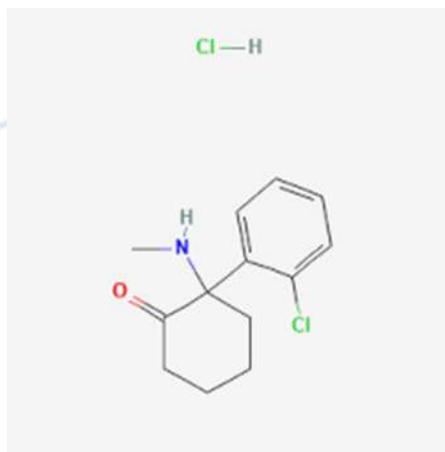
- Ketamine hydrochloride

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## 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.
- Pediatric anesthesia (safe for children).
- Procedural sedation in emergency medicine.