Drugs Acting on Central Nervous System

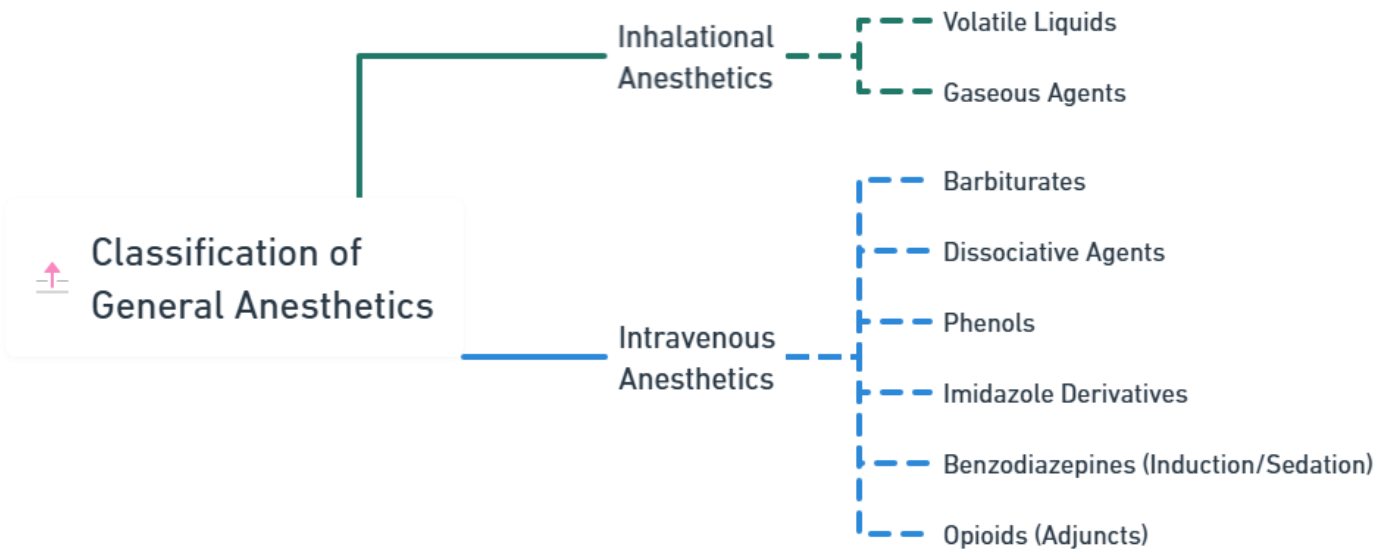
General Anesthetics

Introduction

- General anesthetics are a class of drugs that induce reversible loss of consciousness, analgesia, amnesia, muscle relaxation, and loss of reflexes, typically for the purpose of enabling surgical procedures.
- These agents act on the central nervous system (CNS) and bring about a controlled, temporary state of unconsciousness.
- They are distinct from local anesthetics, which block sensation in a specific area without affecting consciousness.
- General anesthetics are administered either intravenously or via inhalation.

Classification

General anesthetics are broadly classified into two categories based on the **route of administration**:



1. **Inhalational Anesthetics**

   A. **Volatile Liquids:**

   - Halothane
   - Isoflurane
   - Desflurane
   - Sevoflurane
   - Enflurane

   B. **Gaseous Agents:**

   - Nitrous oxide
   - Xenon

2. Intravenous Anesthetics

A. Barbiturates:

- Thiopentone sodium
- Methohexital

B. Dissociative agents:

- Ketamine

C. Phenols:

- Propofol

D. Imidazole derivatives:

- Etomidate

E. Benzodiazepines (used for induction/sedation):

- Midazolam
- Diazepam

F. Opioids (used as adjuncts):

- Fentanyl
- Morphine

Mechanism of Action

- The mechanism is complex and not fully understood but primarily involves modulation of ligand-gated ion channels:
  - **GABA-A receptor potentiation**: Many general anesthetics (e.g., propofol, barbiturates, volatile agents) enhance GABAergic inhibitory neurotransmission, leading to neuronal hyperpolarization and CNS depression.
  - **NMDA receptor antagonism**: Drugs like ketamine and nitrous oxide inhibit NMDA receptors, thereby preventing excitatory neurotransmission.
  - **Two-pore domain K+ channels (TREK-1 activation)**: Some agents activate potassium channels, leading to neuronal hyperpolarization.

Pharmacokinetics

A. Inhalational Agents

- **Absorption**: Through alveoli; depends on solubility in blood (blood-gas partition coefficient).
- **Distribution**: Rapidly to brain due to high perfusion.
- **Metabolism**: Mostly exhaled unchanged; minimal hepatic metabolism.
- **Excretion**: Primarily via lungs.

- *Blood-gas solubility affects onset and recovery:*
  - Lower solubility = faster induction & recovery (e.g., desflurane, sevoflurane).

B. Intravenous Agents

- **Absorption**: Directly into systemic circulation.
- **Distribution**: Rapid onset due to high lipid solubility and rapid CNS penetration.
- **Metabolism**: Mainly hepatic (except etomidate—rapid ester hydrolysis).
- **Excretion**: Renal (as metabolites).

Pharmacodynamics

- **CNS**: Depression of cortical and subcortical centers → unconsciousness, amnesia, analgesia.
- **Cardiovascular**: Varies by drug; some cause hypotension (e.g., propofol), some maintain stability (etomidate).
- **Respiratory**: Respiratory depression common (except ketamine and nitrous oxide).
- **Muscle relaxation**: Often combined with neuromuscular blockers.
- **Others**: Increased intracranial pressure (halothane), emergence reactions (ketamine).

Adverse Effects

Agent	Adverse Effects
Halothane	Hepatotoxicity (halothane hepatitis), arrhythmias
Enflurane	Seizures
Isoflurane	Respiratory depression, hypotension
Nitrous oxide	Diffusional hypoxia, megaloblastic anemia (chronic use)
Ketamine	Hallucinations, increased intracranial pressure
Propofol	Hypotension, respiratory depression, pain at injection site
Etomidate	Adrenocortical suppression

Contraindications

- **Halothane**: Liver disease, susceptibility to malignant hyperthermia
- **Enflurane**: Epilepsy
- **Ketamine**: Increased intracranial pressure, psychiatric illness
- **Propofol**: Hypovolemia, egg allergy (formulation related)
- **Etomidate**: Sepsis (due to adrenal suppression)
- **Nitrous oxide**: Pneumothorax, middle ear surgery, pregnancy (long term use)

Therapeutic Uses

- Induction and maintenance of general anesthesia (IV and inhalational agents)
- Short procedures (e.g., dental, endoscopy): IV agents like propofol, midazolam
- Adjunct to surgical anesthesia: Opioids and benzodiazepines
- Sedation in ICU: Midazolam, propofol
- Electroconvulsive therapy (ECT): Methohexital, propofol
- Pediatric anesthesia: Sevoflurane (pleasant smell, non-irritant)

Drug Interactions

- **Additive CNS depression** with opioids, benzodiazepines, alcohol, antihistamines
- **Halothane** + **succinylcholine** → Malignant hyperthermia
- **Enzyme-inducing drugs** (e.g., phenytoin) may increase metabolism of some agents
- **Beta-blockers or antihypertensives**: Enhanced hypotensive effect with propofol

Dose and Route of Administration

Drug	Route	Usual Induction Dose
Propofol	IV	1.5–2.5 mg/kg
Thiopental	IV	3–5 mg/kg
Etomidate	IV	0.2–0.3 mg/kg
Ketamine	IV	1–2 mg/kg (IV), 4–8 mg/kg (IM)
Midazolam	IV	0.1–0.2 mg/kg
Sevoflurane	Inhaled	2–4% for induction
Isoflurane	Inhaled	1–2% for maintenance
Nitrous Oxide	Inhaled	50–70% in oxygen (often used with other agents)

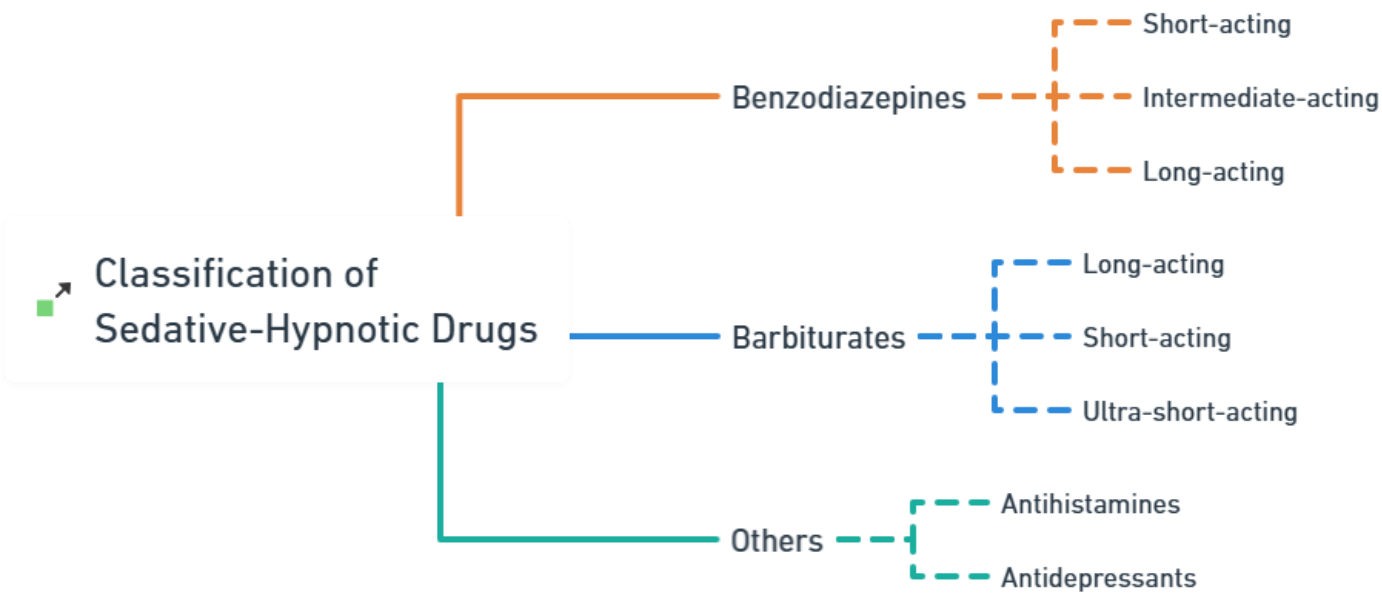
Sedatives

Introduction

- Sedatives and hypnotics are central nervous system (CNS) depressants used to induce calmness (sedation) or sleep (hypnosis). The key distinction lies in dose:
    - **Sedatives**: Produce relaxation, anxiolysis, and decreased activity without causing sleep.
- At higher doses, many sedatives become hypnotics, and at even higher doses, they can lead to anesthesia or coma, depending on the drug class.
- These drugs are primarily used in the management of insomnia, anxiety, seizures, and as preanesthetic medication.

Classification

Based on Chemical Structure and Duration of Action



A. Benzodiazepines

- **Short-acting**: Triazolam, Midazolam
- **Intermediate-acting**: Alprazolam, Lorazepam
- **Long-acting**: Diazepam, Flurazepam

B. Barbiturates

- **Long-acting**: Phenobarbital
- **Short-acting**: Pentobarbital, Secobarbital
- **Ultra-short-acting**: Thiopental

C. Others

- **Antihistamines**: Diphenhydramine, Hydroxyzine

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