Intravenous Anesthesia

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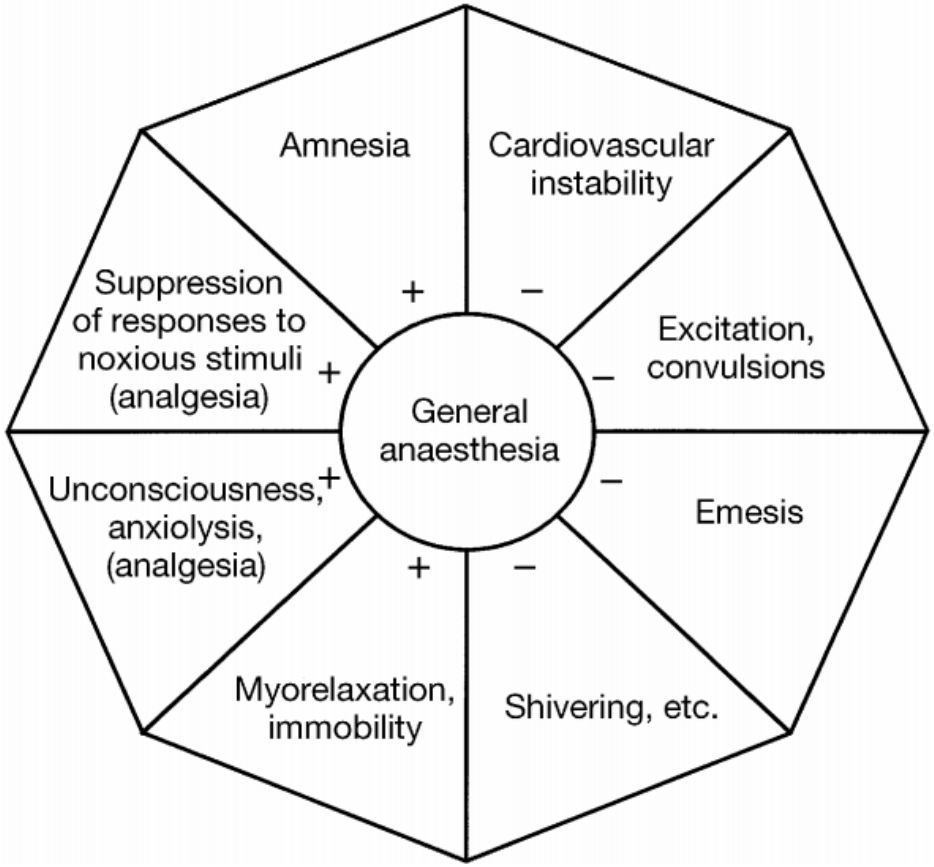
Objectives

- Classification
- Mechanism of action
- Clinical applications
- Adverse effects

Components of General Anesthesia



- Anesthesia
- Analgesia
- Muscle relaxation

B. W. Urban, and M. Bleckwenn. Br. J. Anaseth. 2002; 89:3-16.

Intravenous Anesthetic Agents

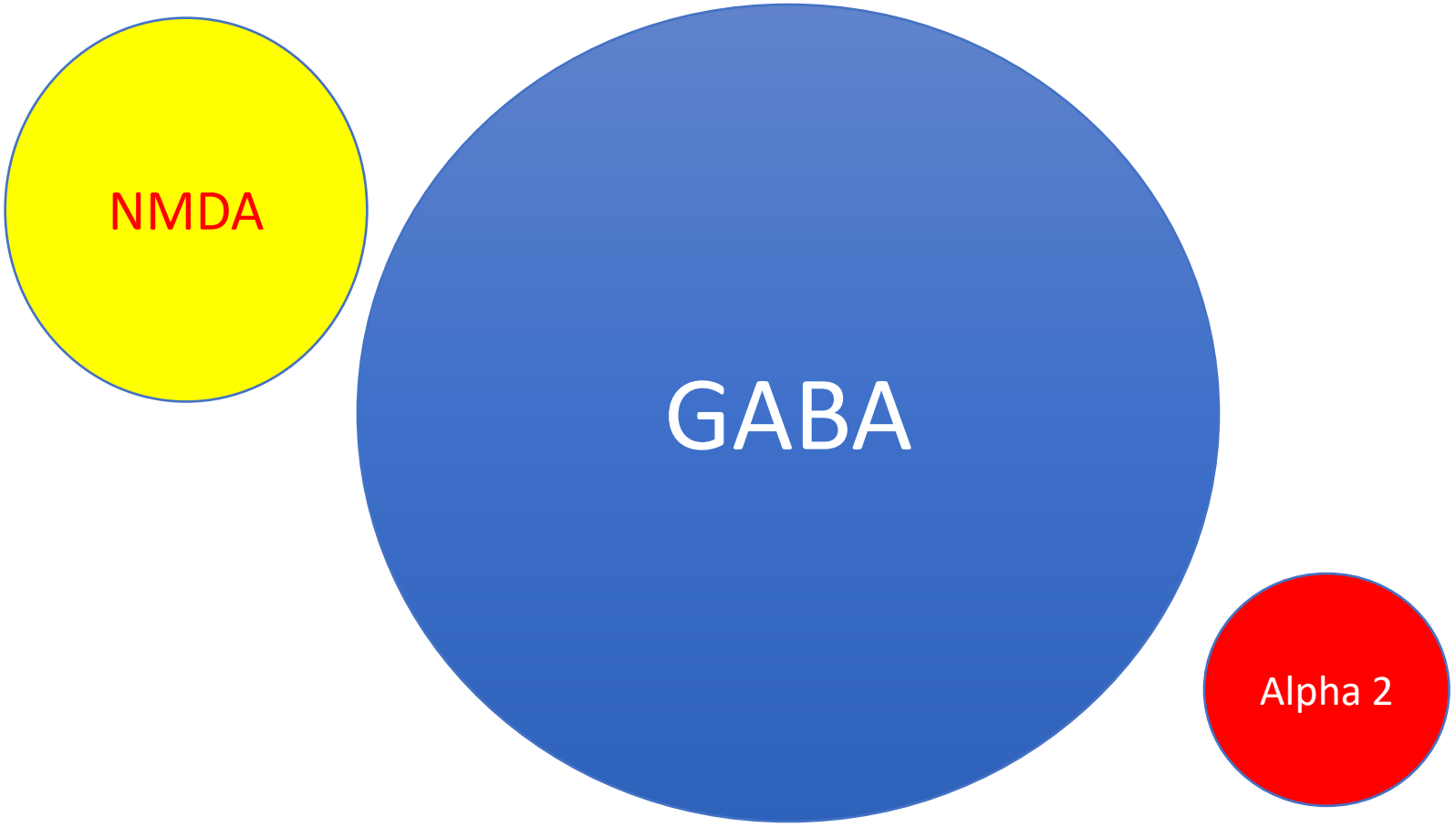
Propofol

Etomidate

Thiopental

Ketamine

Benzodiazepine


NMDA
GABA
Alpha 2

Propofol

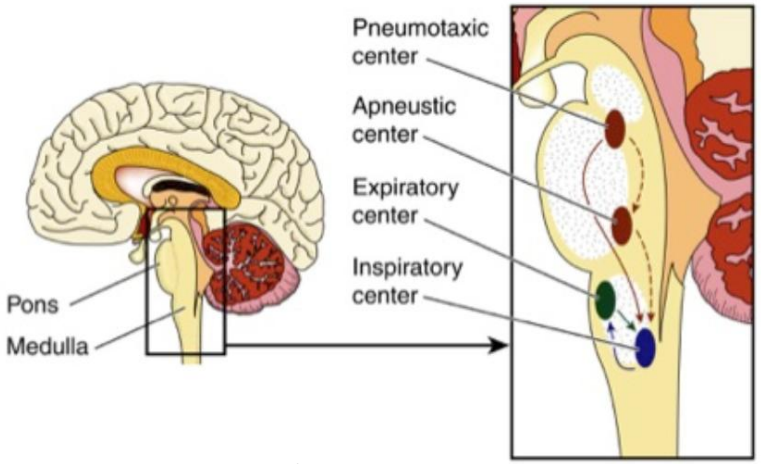
- An egg lecithin emulsion formulation
  - 10% soybean oil, 2%glycerol, 1.2% egg phosphatide
  - Formulations support growth of bacteria
  - Typically 12 hours is critical
- **Pain on injection** occurs in 32-67% of subjects
- 1.5-2.5 mg/kg : Induction dose.

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA: Elsevierj Churchill Livingstone.

Propofol

- CNS
  - $GABA_A$:Hypnotic
  - ↓CMR, CBF, ICP
  - NO analgesia

- Respiratory System
  - ↓ TV > RR
  - ↓ response to hypoxia
  - ↓ response hypercapnia
  - Dose-dependent respiratory depression



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Propofol

- CVS
  - Why does propofol decrese BP on induction?

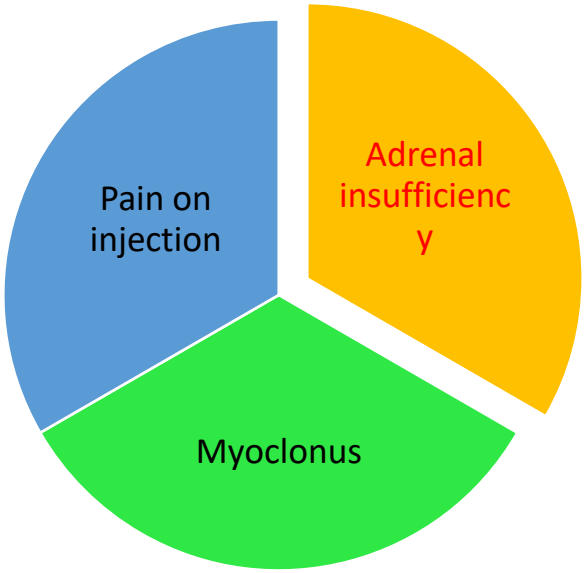
Venodilatation	**+++**
Arterial dilation	+
Decreased sympathetic outflow (and reflex inhibition)	++
Direct myocardial depression	+

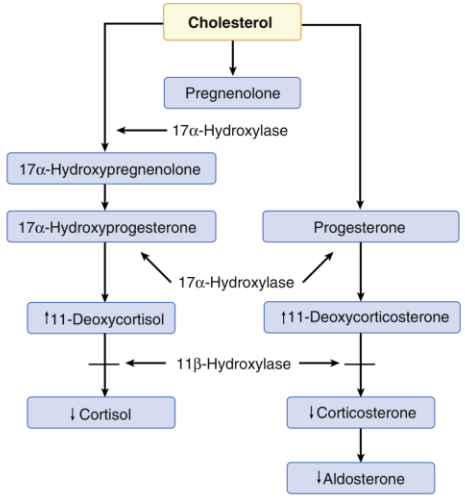
Ebert T. Sympathetic and hemodynamic efforts of moderate and deep sedation with propofol in humans. Anesthesiology. 2005;103:20-24.

Etomidate

- Rapid onset (high lipid solubility)
- Large non-ionized fraction at physiologic pH
- Duration related with dose

Induction Dose (mg/kg)	0.2-0.3
Duration of Action (min)	3-8
T ½ Distribution (min)	2-4
T ½ Elimination (min)	2.9-5.3
Clearance (ml/kg/min)	18-25
Protein Binding (%)	77
Volume of Distribution (L/kg)	2.5-4.5

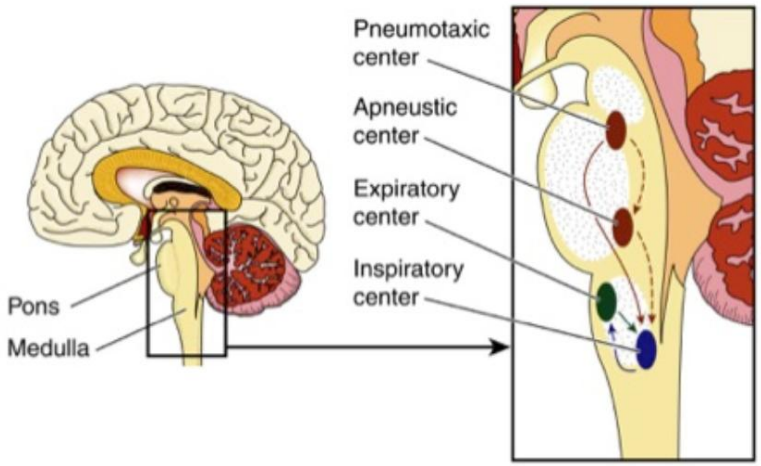




Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Etomidate

- CNS
  - ↓CMR, CBF, ICP
  - Maintained CPP (due to↓ SBP)



- Respiratory System
  - Less depression of respiratory center
- CVS
  - **Maintain hemodynamic stability**
    - Not induce histamine release

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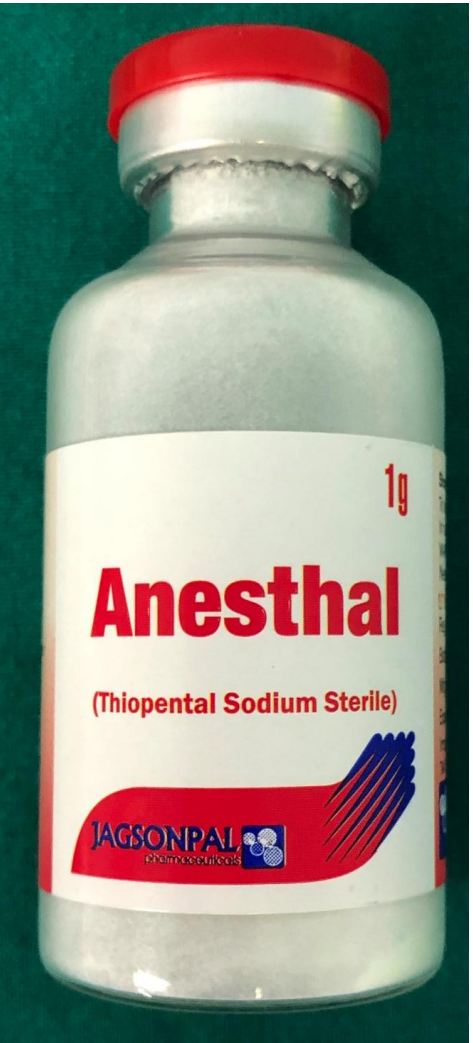
Barbiturates : Thiopental



- Highly alkaline (pH 9)
- Cautions
  - Intra-arterial injection
    - vasoconstriction, thrombosis and tissue necrosis
  - Hepatic and renal disease
  - Patient with acute intermittent porphyria

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Thiopental

Induction Dose (mg/kg)	**3-5**
Duration of Action (min)	**5-10**
T ½ Distribution (min)	**2-4**
T ½ Elimination (min)	**11**
Clearance (ml/kg/min)	**3.4**
Protein Binding (%)	**83**
Volume of Distribution (L/kg)	**1.5-3**

- Hepatic metabolism
- Rapidly redistribution
- Larger doses can saturate peripheral compartments
  - prolonged duration of action

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Thiopental

- CNS
  - GABA agonist
  - Potent cerebral vasoconstrictor
  - ↓CMR, CBF, ICP
- CVS
  - ↓ sympathetic outflow
  - Peripheral vasodilatation
  - ↓ SVR, direct myocardial depressant
- Respiratory System
  - Dose-dependent respiratory depression

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

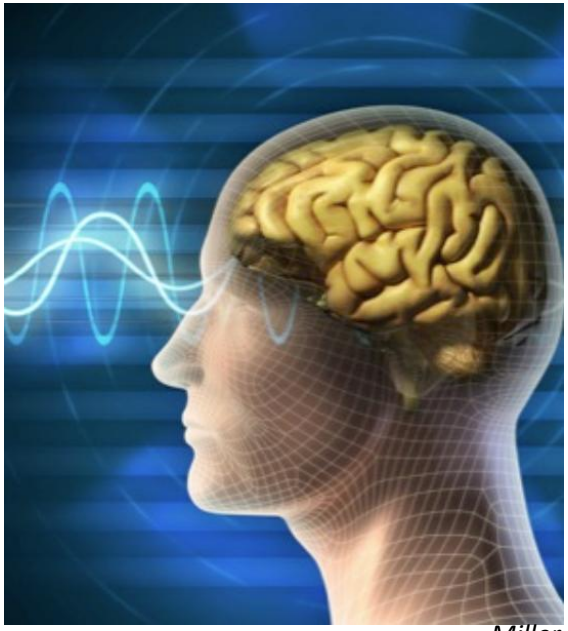
Ketamine

- Phencyclidine derivative
- Potent NMDA antagonist: Significant analgesia
- Metabolized by hepatic CYP3A4 to norketamine (analgesic properties)
- Mixture in USA
  - The S-enantiomer (now available in USA in intranasal formulation for depression) [9]
- Elimination half life 6hr after IV bolus
- Dissociative anesthesia

1.Exp. Rev. Neurother. 19(1),83–92 (2019).
2.Eur. J. Pain 22(4), 632–646 (2018).

Ketamine

- CNS
  - **↑CMR, CBF, ICP**
  - Vivid dreams or hallucination (10-30%)



- Respiratory System
  - Minimal respiratory depression
  - **Preserve airway reflexes**
- CVS
  - **Preserves HR, CO, MAP via sympathetic stimulation**

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Benzodiazepines

- GABA agonist
- Highly lipophilic
- Anxiolytic, amnestic, anticonvulsant properties
- No analgesic property
- Midazolam, Diazepam, Lorazepam
- Flumazenil = specific antagonist
  - Very short acting

Olkkoia KT, Ahonene J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;182:335-60.

Benzodiazepine

- CNS
  - ↓CMR, CBF(Less than propofol)
- CVS
  - HR and CO relatively unchanged
- Respiratory System
  - Dose dependent respiratory depression

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Induction Characteristics and Dosage Requirements for the Currently Available Sedative–Hypnotic Drugs

DRUG NAME	INDUCTION DOSE (mg/kg)	ONSET (sec)	DURATION (min)	EXCITATORY ACTIVITY*	PAIN ON INJECTION*	HEART RATE†	BLOOD PRESSURE†
Thiopental	3–6	<30	5–10	+	0–+	↑	↓
Methohexital	1–3	<30	5–10	++	+	↑↑	↓
Propofol	1.5–2.5	15–45	5–10	+	++	0–↓	↓↓
Midazolam	0.2–0.4	30–90	10–30	0	0	0	0/↓
Diazepam	0.3–0.6	45–90	15–30	0	+/+++	0	0/↓
Lorazepam	0.03–0.06	60–120	60–120	0	++	0	0/↓
Etomidate	0.2–0.3	15–45	3–12	+++	+++	0	0
Ketamine	1–2	45–60	10–20	+	0	↑↑	↑↑

*0 = none; + = minimal; ++ = moderate; +++ = severe.

†↓ = decrease; ↑ = increase.

Clinical Anesthesia 8th; Barash, P.; Lippincott Williams and Wilkins; 2017.

Pharmacokinetic Values for the Currently Available Intravenous Sedative–Hypnotic Drugs

DRUG NAME	DISTRIBUTION HALF-LIFE (min)	PROTEIN BINDING (%)	DISTRIBUTION VOLUME AT STEADY STATE (L/kg)	CLEARANCE (mL/kg/min)	ELIMINATION HALF-LIFE (h)
Thiopental	2–4	85	2.5	3.4	11
Methohexital	5–6	85	2.2	11	4
Propofol	2–4	98	2–10	20–30	4–23
Midazolam	7–15	94	1.1–1.7	6.4–11	1.7–2.6
Diazepam	10–15	98	0.7–1.7	0.2–0.5	20–50
Lorazepam	3–10	98	0.8–1.3	0.8–1.8	11–22
Etomidate	2–4	75	2.5–4.5	18–25	2.9–5.3
Ketamine	11–16	12	2.5–3.5	12–17	2–4

Clinical Anesthesia 8th; Barash, P.; Lippincott Williams and Wilkins; 2017.

Drug	Induction Dose (mg/kg)	Effects	Pearls
Propofol	1.5-2.5	**Neuro:** Decreases cerebral metabolic O2 requirements, cerebral blood flow, intracranial pressure **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose-dependent respiratory depression (apnea in 25-35% of patients)	-Pain on injection (32-67%) -can be attenuated with lidocaine and with injection into larger veins -Antiemetic properties -Anticonvulsant properties
Etomidate	0.2-0.3	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Maintains hemodynamic stability (minimal cardiac depression) **Pulm:** Minimal respiratory depression (no histamine release)	-Pain on injection -High incidence of PONV -Myoclonus -Inhibits adrenocortical axis
Thiopental	3-5	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose-dependent respiratory depression	-Anticonvulsant properties -Can precipitate when injected with acidic fluids (i.e LR)
Ketamine	1-2	**Neuro:** Increases CMRO2, CBF, ICP **CV**: Cardio-stimulating effects (negatively effects myocardial supply-demand) **Pulm:** Minimal respiratory depression; bronchodilation; most likely of all to protect airway reflexes	-Analgesic effects -Intrinsic myocardial depressant effects which may be unmasked with depleted catecholamines

Clinical Anesthesia 8th; Barash, P.; Lippincott Williams and Wilkins; 2017.

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