THE UNIVERSITY OF JORDAN

Intravenous Anesthetics

DR Ahmad Arraqap

Anesthesia dept.

Faculty of Medicine

Jordan University

THE UNIVERSITY OF JORDAN

LECTURE OUTLINE

- ✓ **Introduction**
- ✓ **PHARMACOKINETICS principle**
- ✓ **Pharmacodynamics principle**
- ✓ **General Principles for Intravenous Anesthetics**

THE UNIVERSITY OF JORDAN

General Anesthesia

General Anesthesia clinically implies that:

The patient has been rendered reversibly unconscious by DRUGS

for the execution of a painful operative or diagnostic test.

Subdivisions of General Anesthesia

Are based on the route by which the drug is introduced into the body and thence via the blood stream to the brain:

- *Intravenous.*
- *Inhalational.*
- *Intramuscular.*
- *Rectal.*

What are i.v induction drugs?

- Drugs, when given intravenously in an appropriate dose, cause rapid loss of consciousness.
- Rapid onset : Often described as occurring within **“ ONE ARM-BRAIN CIRCULATION TIME”**
- The time taken for the drug to travel from the site of injection (usually the arm)to the brain, where they have their effect.

Uses of Intravenous anesthetics

- Induction and maintenance of anesthesia
- As a sole anesthetic for short procedures
- Intravenous infusion- to maintain anesthesia for longer procedures e.g. TIVA (Total intravenous anesthesia)
- To provide sedation in places like ICU

Basic Pharmacology Principals

Pharmacokinetics – often times thought of how the body processes the drugs.

- *Key components include Administration (absorption), Distribution, and drug metabolism and excretion.*

Pharmacodynamics - Is often thought of how a drug causes physiological and pharmacological reactions within the body.

- *Reponses on receptors at the cellular level.*

PHARMACOKINETICS

- Defines the relationships among drug dosing, drug concentration in body fluids and tissues, and time .

- Absorption,
- Distribution,
- Biotransformation(METABOLISM)
- Excretion

Absorption

- The processes by which a drug moves from the site of administration to the bloodstream.
- Routes: there are various ways of administering drugs GI tract, transdermal, transmucosal, subcutaneous, intramuscular and intravenous.

- Absorption is influenced by
- The physical characteristics of the drug (solubility, p*K* a , diluents, binders, and formulation),
- Dose
- The site of absorption (eg, gut, lung, skin, muscle).
- Bioavailability is the fraction of the administered dose reaching the systemic circulation.

➢ **First pass metabolism**:

Drugs passing through the GI system will also pass through the portal venous system before entering systemic circulation. Consequently, there is extensive metabolism by liver.

➢ IV administration where it's 100% bioavailable

➢ There is a higher dose requirement for enteric administration of drugs.

Distribution

❖systemic circulation to target organs.

- **Free fraction and protein binding**: most drugs are protein bound making them therapeutically inactive, the free portions, are active.

- **Vd** – is the *apparent* volume into which a drug has "distributed" (ie,mixed).

$$V_d = \frac{\text{Bolus dose}}{\text{Concentration}_{time0}}$$

- Organs are divided according to blood perfusion:

✓ High- perfusion organs (vessel-rich); brain takes up disproportionately large amount of drug

✓ low perfused areas (muscles, fat, and vessel-poor groups).

- After IV injection, vessel-rich group takes most of the available drug
- After highly perfused organs are saturated during initial distribution, the greater mass of the less perfused organs continue to take up drug from the bloodstream.
- As plasma concentration falls, some drug leaves the highly perfused organs to maintain equilibrium.

THE UNIVERSITY OF JORDAN

Tissue Group	Composition	Body Mass (%)	Cardiac Output (%)
Vessel-rich	Brain, heart, liver, kidney, endocrine glands	10	75
Muscle	Muscle, skin	50	19
Fat	Fat	20	6
Vessel-poor	Bone, ligament, cartilage	20	0

- **Redistribution**: some drugs will quickly distribute into certain parts of the body (brain and heart) and slowly into adipose tissue. Once more and more distribution occur into adipose tissue however, equilibrium will force them out of brain and heart, leading to less therapeutic effect.

- This redistribution from the vessel-rich group is responsible for termination of effect of many anesthetic drugs.

Biotransformation

- Biotransformation is the chemical process by which the drug molecule is altered in the body.

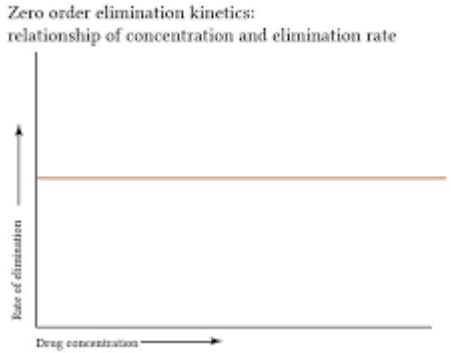
- The liver is the primary organ of metabolism for drugs.

Excretion

- It is the pharmacokinetic term that describes all the processes that remove a drug from the body.
- Liver and the kidneys are considered the major organs of drug elimination
- Drug metabolism can occur at many other locations that contain active drug-metabolizing enzymes (e.g., pulmonary
- vasculature, red blood cells),
- Drug can be excreted unchanged from other organs (e.g., lungs).

Metabolism and Excretion – most excretion occurs through liver, kidney and lungs.

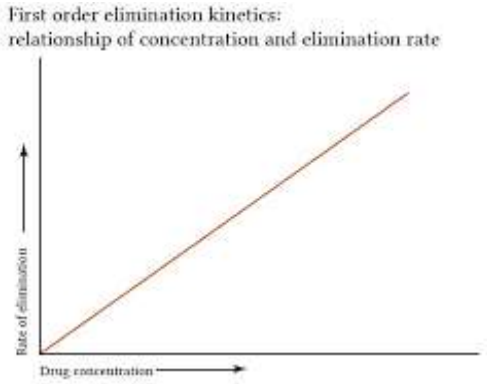
- **Zero-order kinetic** – drugs is metabolized at a fixed rate, regardless of concentration



- **First-order kinetic** – most drugs are metabolized through this process, where rate of metabolism is proportional to concentration.

  Drugs half time – where 50% of drug is eliminated.

  5 half-times is equivalent to 96.9% of drug elimination

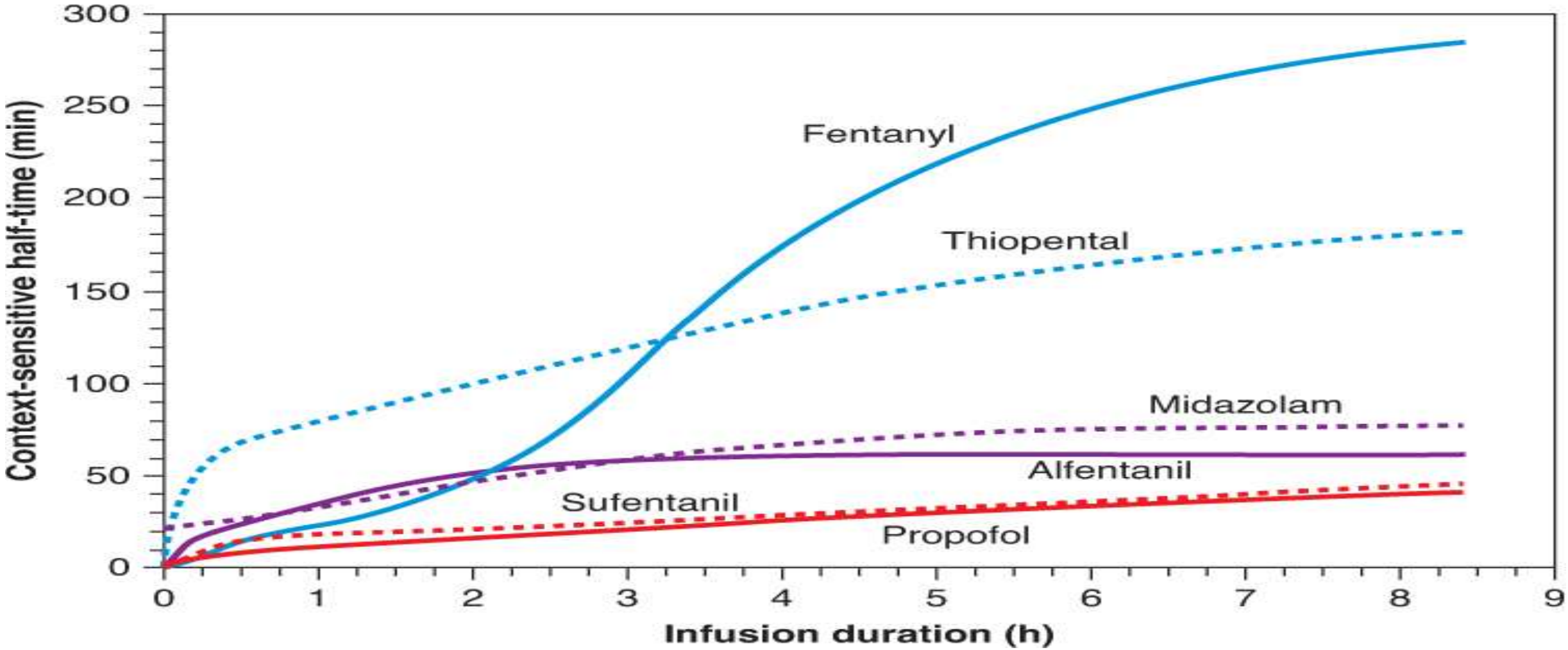


- Elimination half-time (t½) It is the time it takes for the plasma concentration of a drug to decrease to 50% of its original concentration.

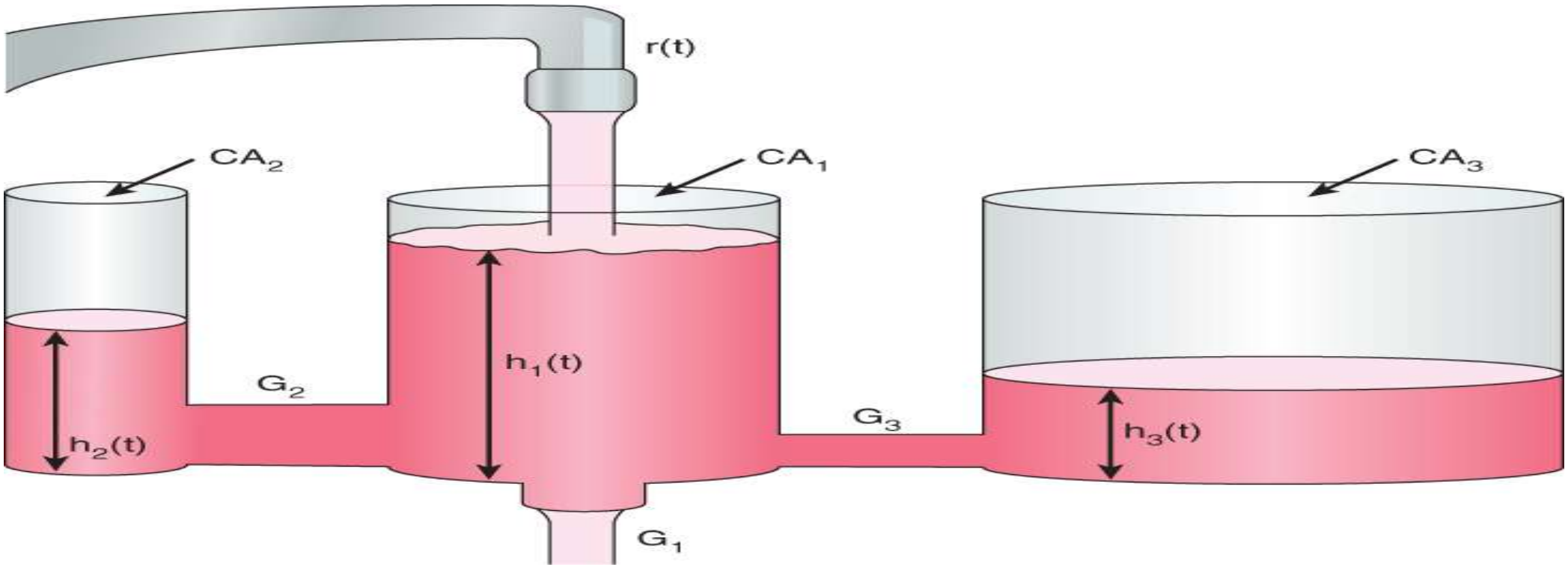
- Context-sensitive half-time is defined as the time to achieve a 50% reduction in concentration after stopping a continuous infusion.

- Context sensitive half-time demonstrates the influence of the distributive process in governing drug disposition.

THE UNIVERSITY OF JORDAN



Hydraulic depiction of a three-compartment model.



Pharmacodynamics

- Is often thought of how a drug causes physiological and pharmacological reactions within the body.
- **Mechanism of action** is a medical term that describes how a medication works in the body.
- A drug's **mechanism of action** may refer to how it affects a specific receptors
- Drugs have agonistic or antagonistic effects on receptor sites.

Pharmacodynamics

- **Potency**: refers to the dose of the drug required to achieve a therapeutic effect.
- **Efficacy**: refers to the maximum effect achievable with the drug.
- **Toxicity**: Drug toxicity occurs when undesirable side- effects of its administration occur.
- **Therapeutic index**: is the ratio of the dose producing a toxic effect to that producing a therapeutic effect.

Classification

- The commonest drugs currently in use can be classified according to their chemical structure and include:

1. Barbiturates – THIOPENTAL, METHOHEXITAL
2. Phenols - PROPOFOL
3. Imidazoles - ETOMIDATE
4. Phencyclidines - KETAMINE
5. Benzodiazepines – MIDAZOLAM, DIAZEPAM, LORAZEPAM
6. Dexmedetomidine

MOA

- Either stimulates an inhibitory neurons or inhibits an excitatory neurons.

- The primary mechanism for **most IV anesthetics** is potentiation of GABA receptors. GABA is the primary inhibitory neurotransmitter in the CNS. Increased chloride conductance across membrane and into postsynaptic neuron promotes hyperpolarization, thus inhibiting neuronal signaling. This has a sedative and hypnotic effect on the individuals.

- Other IV anesthetic mechanisms –

  Ketamine (exerts effect through inhbiting NMDA receptor)
  Dexmedetomidine (Alpha-2-receptor activation)

Barbiturates

- Most commonly used are thiobarbiturates (thiopental) and oxybarbiturate (methohexital)
- Induction Dose: 3 – 5 mg/kg adults
- Each vial contain 0.5 g powder of STP.
- Highly alkaline (pH ~ 10) at 2.5% solution.
- Onset: 30-60 secs after administration >> “arm brain” circulation time
- Enhance $GABA_A$ receptor transmission
- Leads to prolonged cognitive effects compared to Propofol: it decreases cerebral metabolic rate of oxygen (CMRO2), Cerebral blood flow (CBF) and intracranial pressure (ICP).
- Undergo terminal elimination via hepatic metabolism.
- Should not be used in patient with porphyria – will stimulate porphyrin formation and lead to acute crisis.

THE UNIVERSITY OF JORDAN

Table 19-11 Barbiturates

Key Pharmacology	Key Clinical Uses
GABA-A receptor agonist	Induction of general anesthesia
Prolonged context-sensitive half-time	Methohexital used for sedation, premedication and electroconvulsive therapy
CNS depressant, neuroprotective, anti-convulsant, decreases CMRO2, CBF, and ICP	Barbiturate coma (thiopental)
EEG burst suppression (thiopental)	Thiopental intra-arterial injection can lead to tissue necrosis
Cardiovascular: decreases mean arterial pressure, venous vascular tone, and cardiac output	
Pulmonary: dose-dependent respiratory depression, does not cause bronchodilation	

CBF, cerebral blood flow; CMRO2, cerebral metabolic oxygen consumption rate; EEG, electroencephalogram; GABA-A, gamma-aminobutyric acid-A; ICP, intracranial pressure.

Propofol

- Induction Dose: 1.5– 2.5 mg/Kg
- 1% pre-prepared ampules
- Increases binding affinity of GABA with GABAA receptor.
- Onset: 30-60 secs after administration >> "arm brain" circulation time
- Produced in an 1% egg lecithin emulsion, glycerol and soybean oil (relevant to patient allergies to egg white – not contraindicated with egg allergy).
- Formulation can support bacterial growth – need for good sterile technique
- Highly lipid soluble – only administered intravenously
- Half-life of 2 – 8 minutes
- Rapid hepatic metabolism to water soluble compound and removed by kidneys

Propofol

- Potent cardiovascular and respiratory depressant
- Decreases BP by decreasing cardiac contractility, SVR and preload (inhibition of sympathetic tone and direct vascular smooth muscle effect).
- The most profound cardio depressant of all induction agents.
- Avoid in cases where the patient is hypotensive already or unable to maintain hemodynamic stability.
- In 2/3 of patient is there also pain on injection. Co-administration of 1% lidocaine can lessen the pain.
- Has antipruritic and antiemetic properties – used in TIVA (total intravenous anesthesia) and as background infusion to prevent PONV (post op nausea & vomiting)

Table 19-2 Propofol

Key Pharmacology	Key Clinical Uses
Primary mechanism: GABA-A receptor agonist	General anesthesia induction and maintenance
Predictable context-sensitive half-time across various comorbidities	Commonly used for TIVA
CNS depressant, neuroprotective, anticonvulsant, decreases CMRO2, CBF, and ICP	Conscious and deep sedation, including out-of-operative-room settings
Can be used for EEG burst suppression	Intensive care unit sedation
Cardiovascular: Significant decreases in systemic vascular resistance, stroke volume, and cardiac output	Postoperative nausea and vomiting prophylaxis
Pulmonary: Respiratory depressant and potent bronchodilator	Safe for use in patients with malignant hyperthermia
Addiction potential: May elicit feelings of well-being or euphoria during emergence	
Side effects: Associated pain with injection, propofol infusion syndrome	

CBF, cerebral blood flow; CMRO2, cerebral metabolic oxygen consumption rate; CNS, central nervous system; EEG, electroencephalogram; GABA-A, gamma-aminobutyric acid-A; ICP, intracranial pressure; TIVA, total intravenous anesthesia.

Etomidate

- Induction dose: 0.2 – 0.3 mg/kg
- 2mg/ml solution
- Can cause irritation and pain on injection.
- Lidocaine pre-administration will help.
- Acts through binding to $GABA_A$ receptors
- decreases CMRO2, CBF and ICP while maintaining good CPP.
- Superior hemodynamic stability compared with other induction agents. Etomidate does not cause vasodilation or myocardial depression
- PONV is common.
- Transiently inhibits 11-B-hyroxlase, an enzyme involved with production of steroids – can cause adrenal suppression.
  - Inhibition lasts for 4 – 8 hours, worse with infusions

THE UNIVERSITY OF JORDAN

Table 19-3 Etomidate

Key Pharmacology	Key Clinical Uses
GABA-A receptor agonist	Hemodynamically stable induction
Hemodynamically stable	Cardiac, trauma, and hypovolemic patients
Adrenocortical suppression	
Postoperative nausea and vomiting	

GABA-A, gamma-aminobutyric acid-A.

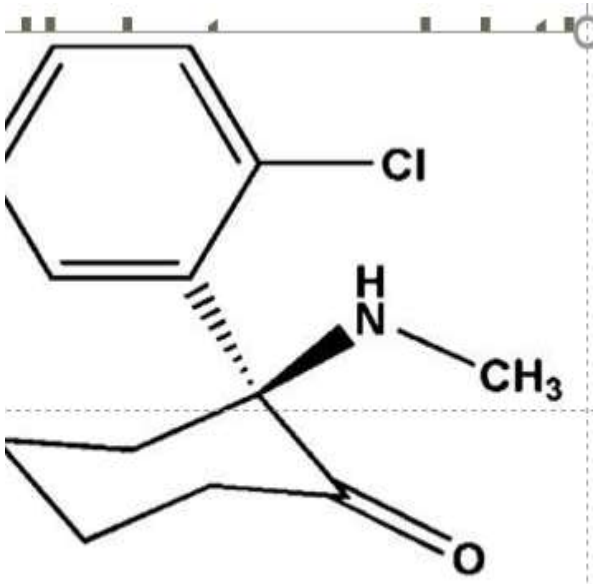
Ketamine

- Dose: 1 to 2 mg/kg IV .

  The IM induction dose is 4 to 6 mg/kg.
- Several routes of administration: IV, IM, Oral, Rectal, epidural and intrathecal
- Mechanism through NMDA (Causes analgesia by blocking pain signals at spinal cord but also disassociating the signal between thalamus and limbic system.
- Dissociative amnesia – patient appear conscious (eye open, staring) but unresponsive to sensory input (pain, verbal, stimulus)
- Can causes unpleasant emergence reactions with hallucination and fear.
- N-Methyl-D-aspartate) receptor antagonism.

Ketamine

- Stimulates sympathetic nervous system
- Has minimal respiratory depression
- Causes potent bronchodilation
- Increases CBF, CMRO2, ICP.
- Direct myocardial depressant but indirectly increases catecholamines resulting in increased blood pressure, heart rate and cardiac output.
- Relative contraindication in patients with space-occupying CNS lesions



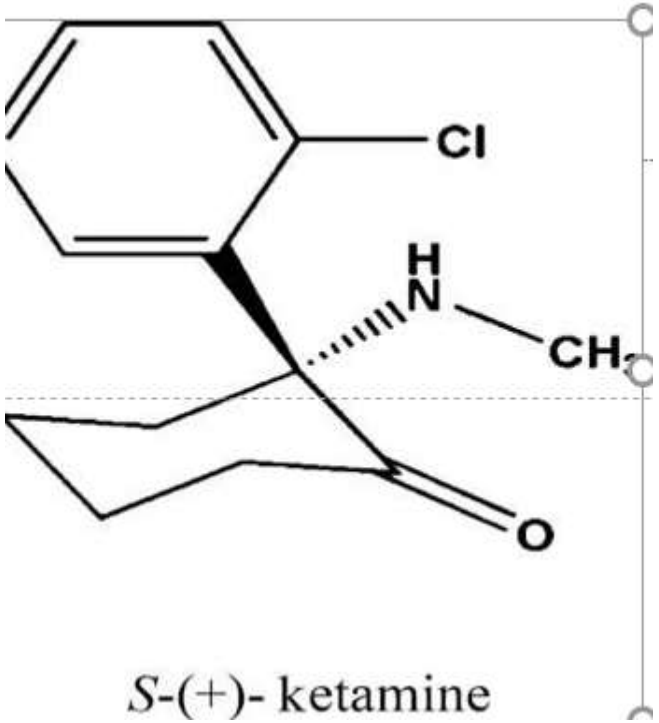
R-(–)- ketamine

Presence of asymmetric carbon atom results in the existence of two **OPTICAL ISOMERS of ketamine: S(+) & R(-) forms**

Most frequently used preparation of ketamine – Racemic mixture

S(+) ketamine produces (when compared to R(-) form):

a) More intense analgesia
b) More rapid metabolism & thus recovery
c) Less salivation
d) Lower incidence of emergence reactions



S-(+)- ketamine

THE UNIVERSITY OF JORDAN

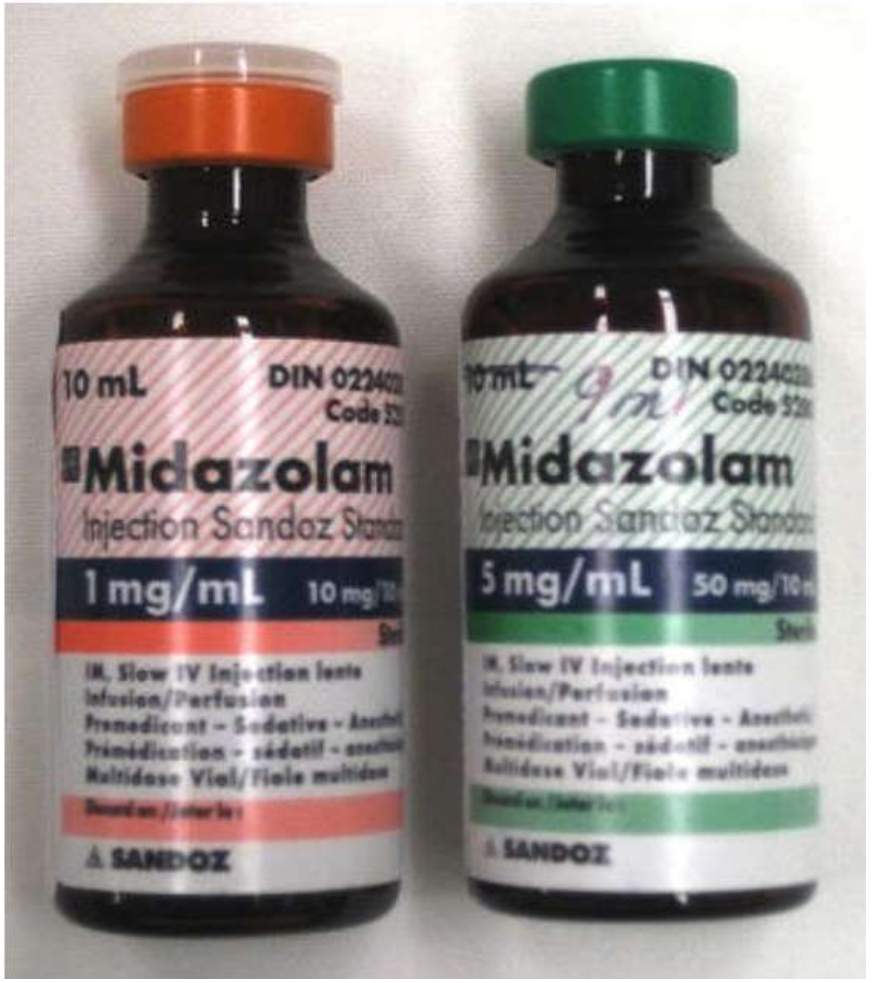
Table 19-5 Ketamine

Key Pharmacology	Key Clinical Uses
NMDA receptor antagonist	Anesthesia—intravenous and intramuscular induction
Cardiovascular stability; increases heart rate and blood pressure	Analgesia
Mild respiratory depression	Chronic pain
Side effects: Emergence delirium, hallucinations, nystagmus, increased salivation	Depression
Trance-like cataleptic unconscious state ("dissociative anesthesia")	Bronchodilator
	Procedural sedation, especially in pediatric and burn patients

NMDA, N-methyl-D-aspartate.

Benzodiazepines

- Commonly used benzos are: Midazolam , Diazepam and Lorazepam
- All benzos have anxiolytic, amnestic, sedative, hypnotic, anticonvulsant properties. NOT analgesic.
- Bind to same $GABA_A$ receptors as barbiturates but at different site on receptor
- Produce mild respiratory, cardiovascular and upper airway reflex depression
- Usually given as premedication, sedation and anxiolysis before GA
- Half-life of 3 hrs
- Dose for Midazolam
  - Premedication: 0.04 – 0.08 mg/kg IV (1-2 mg)
  - Induction dose 0.1 – 0.2 mg/kg IV



- Unlike Propofol and barbiturates, sedation can be reversed by administration of ***FLUMAZENIL***
- Specific competitive antagonist with high affinity for benzo receptors

Table 19-7 Benzodiazepines

Key Pharmacology	Key Clinical Uses
GABA-A receptor agonist	Anxiolysis
Minimal respiratory depression	Anterograde amnesia
Minimal cardiovascular depression	Sedation
Large therapeutic window	Induction of anesthesia, hemodynamically stable
Reversible with flumazenil	Anticonvulsant

GABA-A, gamma-aminobutyric acid-A.

THE UNIVERSITY OF JORDAN

Table 19-8 Benzodiazepine Metabolism and Clearance

Drug	Duration	Metabolites	Hepatic Clearance
Midazolam	Short	1-hydroxymidazolam (mild CNS depressant)	High
Diazepam	Intermediate	Oxazepam and desmethyldiazepam	Slow
Lorazepam	Long	Inactive	Intermediate

CNS, central nervous system.

THE UNIVERSITY OF JORDAN

Table 19-10 Midazolam Dosing by Clinical Use

Premedication: (anxiolysis/anterograde amnesia)	0.02–0.04 mg/kg IV/IM; 0.4–0.8 mg/kg PO
Induction: (hypnosis/amnesia/sedation)	0.1–0.2 mg/kg IV
Infusion (in conjunction with volatile anesthetics): (hypnosis/amnesia)	0.25–1 mcg/kg/min

IM, intramuscular; IV, intravenous; PO, oral.

Dexmedetomidine (Precedex)

- Highly selective alpha-2 adrenergic agonist
- Sedation and analgesia without much respiratory depression
- Half-life of 2 hrs.
- Dose:
  - Loading dose: 0.5 – 1 mcg/kg over 10 minutes
  - infusion dose: 0.2 – 0.7 mcg/kg
- Has <u>sedative, analgesic, sympatholytic, and anxiolytic effects</u>
- Sedation for awake fiberoptic intubation, regional anesthesia or as an adjunct to general anesthesia. In ICU, to wean patients off ventilator

THE UNIVERSITY OF JORDAN

Table 19-6 Dexmedetomidine

Key Pharmacology	Key Clinical Uses
Alpha-2-adrenergic agonist	Intensive care unit sedation in mechanically ventilated patients
Sedation with minimal respiratory depression	Procedural sedation
Mimics normal sleep pattern on EEG	Pediatrics: preoperative anxiolysis and emergence delirium
Provides analgesia at the spinal cord level	
Administration: bolus 0.5–1 mcg/kg over 15 min, followed by 0.3–0.7 mcg/kg/h infusion	
Side effects: bradycardia and hypotension	

EEG, electroencephalogram.

Drug	CVS			RS	CNS		
	HR	SVR	MAP	Ventilation	CBF	CMRO2	ICP
Barbiturate	+	-	--	---	---	---	---
Propofol	0	--	---	---	---	---	---
Benzodiazepines	+	-	-	--	--	--	--
Etomidate	0	0	0/-	-	---	---	---
Ketamine	++	0	++	0/-/+	+++	+	+++

Drug	Speed of Induction and Recovery	Pain on injection	Delirium	PONV	analgesia
Thiopental	Fast Accumulation occurs, giving slow recovery	No	-	0	-- antanalgesic
Etomidate	Fast onset Fairly fast recovery	Yes	-	+	0
Propofol	Fast onset, Very fast recovery	Yes	-	--	0
Ketamine	Slow onset	No	++	++	++
Midazolam	Slower than other agents	No	-	0	0

- New drugs are constantly being developed in an effort to achieve the ideal intravenous anesthetic .

Examples:

- Remimazolam.
- *Fospropofol*
- *Cyclopropyl-methoxycarbonyl metomidate (CPMM).*
- THRX-918661/AZD-3043.

THE UNIVERSITY OF JORDAN

Table 19-1 Properties of the Ideal Intravenous Anesthetic Agent

Pharmacodynamic/Pharmacokinetic Properties
Hypnosis and amnesia
Rapid onset (time of one arm-brain circulation)
Rapid metabolism to inactive metabolites
Minimal cardiovascular and respiratory depression
No histamine release or hypersensitivity reactions
Nontoxic, nonmutagenic, noncarcinogenic
No untoward neurological effects, such as seizures, myoclonus, antanalgesia, neurotoxicity
Other beneficial effects: analgesia, antiemetic, neuroprotection, cardioprotection
Pharmacokinetic-based models to guide accurate dosing
Ability to continuously monitor delivery
Physiochemical Properties
Water-soluble
Stable formulation, nonpyrogenic
Nonirritating: painless on intravenous injection
Small volume needed for induction
Inexpensive to prepare and formulate
Antimicrobial preparation

Thank You