

Neuropsychiatry Block

Pharmacology Team 439



[Helpful video](#)

General Anesthetics

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Objectives:

- 1- Define anesthesia, balanced anesthesia, and preanesthetic medication.
- 2- Be able to define MAC, potency, blood: gas partition coefficient and oil: gas partition coefficient.
- 3- Distinguish between inhalation and intravenous anesthetics.
- 4- Identify the pharmacokinetics, pharmacological actions, and side effects of inhalation anesthetics.
- 5- Identify the pharmacokinetics, pharmacodynamics, and side effects of intravenous anesthetics.
- 6- Know the difference between neuroleptanalgesia and neuroleptanesthesia.

Introduction

General Anesthetics:

Drugs used to induce **loss of pain sensation, loss of consciousness**, skeletal muscle relaxation, analgesia, amnesia (to forget events of the operation) and inhibitions of **undesirable autonomic reflexes** e.g. Bradycardia. It's a definition of an ideal general anesthetic. In reality there is no single drug that can achieve all of this so patients are given a combination of drugs to achieve this goal.

Types of anesthesia

General anesthesia

Focus of this lecture

Local anesthesia

Cocaine derivatives e.g. Lidocaine

Characters of an ideal anesthetic drug:

1

Smooth & rapid induction

Smooth: able to bypass the first two stages of anesthesia and reach stage III

3

Wide safety margin

2

Rapid recovery

4

Minimal side effects

Balanced Anesthesia

The use of more than one drug in combination to fulfil the patient needs, thus it will:

↑ beneficial effects, ↓ adverse effects

It's achieved by a combination of:

1- **I.V** anesthesia

2- **Inhaled** anesthesia

3- **Pre-anesthetic** medications (given sometimes).

Stages of Anesthesia Progressive CNS depression

Stage I
Analgesia

- Loss of pain sensation.
- The patient is conscious and conversational.

Stage II
Excitement

- Irregular Stage
- ↑ Respiratory rate.
- ↑, Irregular BP.
- Patient may experience delirium & violent behavior.
- **Eye dilated & reactive** (light → miosis).

Stage III
Surgical Anesthesia

- Stable Stage where operation is running
- The goal is to reach this stage ASAP, and stay here
- **Regular** respiration & relaxation of skeletal muscles.
- Eye reflexes ↓ until the pupil is fixed (**NOT reactive**).

Stage IV
Coma & Death

- Undesirable stage, avoid reaching it
- Medullary paralysis.
- Severe depression of vasomotor.
- Depression of respiratory centers.
- Death may occur.

	RESPIRATION		OCULAR MOVEMENT	PUPIL SIZE (no pre-medication)	EYE REFLEXES	MUSCLE TONE	RESPIRATORY RESPONSE TO SKIN INCISION
	inter-costal	diaphragmatic					
STAGE I: ANALGESIA	Normal		Voluntary control	Normal	Normal		
STAGE II: EXCITEMENT					Lid	Tense struggle	
STAGE III: SURGICAL ANESTHESIA	Plane 1		No eye motion		Corneal		
	Plane 2						
	Plane 3						
	Plane 4						
STAGE IV: IMMINENT DEATH	Apnea				No light reflex	Flaccid	

Pre-Anesthetic Medications

- Medications given to patient before the use of anesthetics immediately before the operation.
- Calm the patient (Anxiolytics) & relieve pain (Opiates).
- Protect against undesirable effects of the subsequently administered anesthetics or the surgical procedure (Antihistamines).
- Facilitate smooth induction of anaesthesia.
- Lower the dose of anaesthetic required.
- All of them are frequently used except opiates & thiopental, which are only used occasionally.
- These are not required. They are add ons that are decided by the anesthesia team.

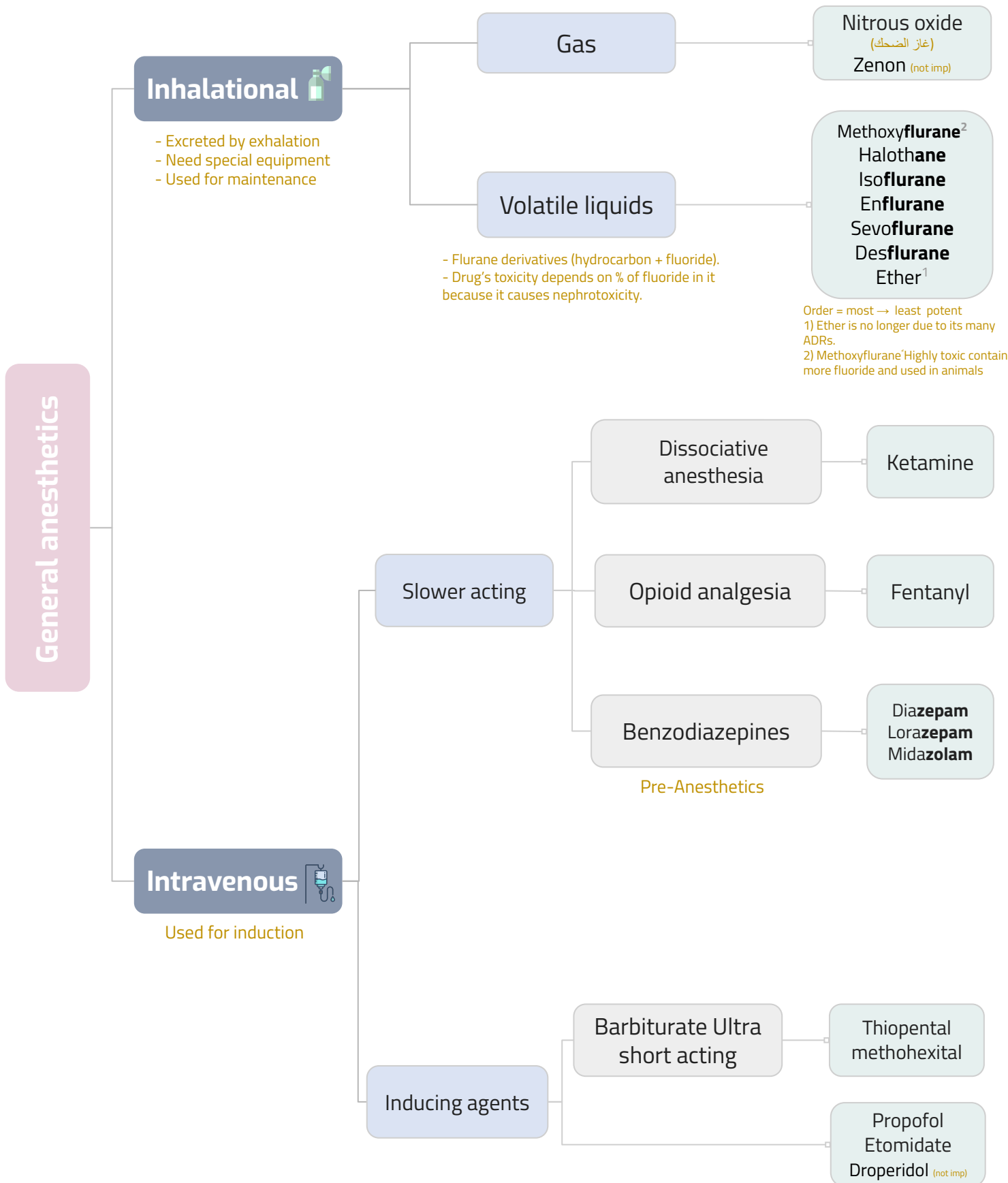
Drugs	Uses	Examples
Opiates	Induce analgesia	Morphine
Anticholinergics	Prevent secretion of fluids into the respiratory tract parasympathetic antagonist = inhibit secretion. So aspiration of fluids is avoided leading to decrease in the vagomimetic action on the heart and bradycardia is eventually avoided.	Hyoscine preferred over atropine because:- 1- Antiemetic (helps with post-operative nausea and vomiting). 2- Prevent bradycardia during the operation. 3- Prevent secretion of fluids into the respiratory tract. 4- More sedative than atropine.
Sedatives & anxiolytics	Relieve anxiety Relieve aggression in delirium (stage II)	Diazepam
Antihistamines	Allergic reactions	Diphenhydramine
Antiemetics	Post surgical nausea & vomiting.	Metoclopramide & prochlorperazine
H2-receptor blockers	Reduce gastric acidity (prevent aspiration of gastric acid).	Ranitidine
Thiopental (Barbiturates) Can be used alone as I.V	Smooth induction	-

Adjuncts to general anesthesia

Neuromuscular blockers #MSK: Skeletal Muscle Relaxant	- Facilitate intubation - Suppress muscle tone	Succinylcholine, vecuronium & atracurium given if the anesthetic drug doesn't cause skeletal muscle relaxation.
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Overview

ALL ARE CNS DEPRESSANT



General anesthetics

Inhalational

- Excreted by exhalation
- Need special equipment
- Used for maintenance

Gas

Nitrous oxide

(غاز الضحك)

Zenon (not imp)

Volatile liquids

- Flurane derivatives (hydrocarbon + fluoride).
- Drug's toxicity depends on % of fluoride in it because it causes nephrotoxicity.

Methoxyflurane²

Halothane

Isoflurane

Enflurane

Sevoflurane

Desflurane

Ether¹

Order = most → least potent
1) Ether is no longer due to its many ADRs.
2) Methoxyflurane² Highly toxic contain more fluoride and used in animals

Intravenous

Used for induction

Slower acting

Dissociative anesthesia

Ketamine

Opioid analgesia

Fentanyl

Benzodiazepines

Diazepam
Lorazepam
Midazolam

Pre-Anesthetics

Inducing agents

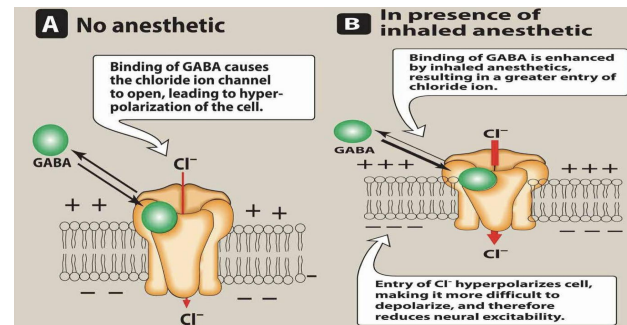
Barbiturate Ultra short acting

Thiopental
methohexital

Propofol
Etomidate
Droperidol (not imp)

MOA of General anesthetics Be it IV or inhalation

Enhance the action of GABA A & glycine on receptors → opening of Cl^- channel → Hyperpolarized neuronal cell → thus ↓ neuronal excitability.



Inhalation anesthetics

Induction
"Onset of Action"

Time elapsed between onset of administration of anesthetics and development of effective surgical anesthesia.

Maintenance
"Sustained Action"

Time during which the patient is surgically anesthetized.

Recovery

Time from discontinuation of anesthetic drug until consciousness is regained.

P.K of Inhalational anesthetics

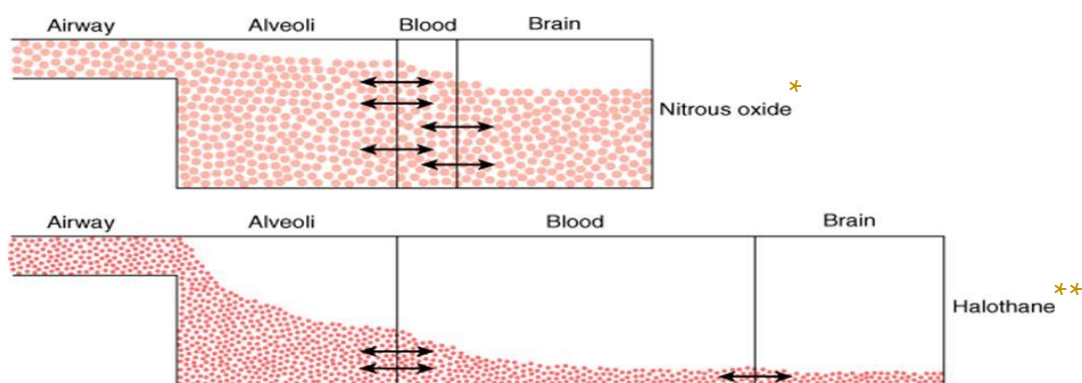
Rate of induction (stage III)

Depth of anesthesia & recovery

Factors controlling induction & recovery

- The anesthetic concentration in the inspired air (**Direct**) i.e. \uparrow conc. \rightarrow \uparrow induction
- Rate & depth of ventilation (**Direct**) i.e. \uparrow Rate & depth of ventilation \rightarrow \uparrow induction
- Blood solubility = Blood:gas (or volatile liquid) partition coefficient **معامل التوزيع (Inverse relation with induction)** i.e. \uparrow Blood solubility \rightarrow \downarrow induction.

Solubility and induction of anesthesia



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>
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Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

*Low Solubility \rightarrow won't stay in blood and **goes directly** to CNS

High Solubility \rightarrow **stays in blood instead of going directly CNS.

Minimum alveolar concentration (MAC)

The concentration of inhalation anesthetic that produce immobility (loss of pain sensation) in **50%** patients in response to surgical operation. Recall #Foundation ED50

- The lower the MAC value the more potent the drug (inverse relation).
- MAC value \uparrow with CNS stimulants (coffee) & \downarrow with CNS depressants (alcohol/morphine).

Prof Hanan: "10mg of a drug produce same effect as 50mg of another drug, the drug preferred here is the one with lower conc. to avoid side effects". i.e. if 10mg would do it then it's best not to increase the dose to avoid ADRs

Inhalation anesthetics

Prof: Numbers are just for understanding the concept

Solubility and Potency increase as you go up
 Induction & recovery and MAC value increase as you go down

Drugs <small>HaloEnIso SevoDes</small>	↑ Solubility	↓ Induction & recovery	↓ MAC value <small>represents the concentration of the gas within the gas tank used for the patient.</small>	↑ Potency
Methoxyflurane <small>Not used anymore</small>	12 <small>(It's only used in animals due to its high nephrotoxicity, so we consider halothane to be the most soluble)</small>	Slow	Low MAC value 0.16	Most potent
Halothane <small>(Pleasant smell)</small>	2.3 <small>(most soluble)</small>	Slow	0.75	Potent
Enflurane <small>(Pungent smell)</small>	1.8	Medium	1.7	Less potent
Isoflurane	1.4	Medium/Rapid	1.4	Less potent
*DOC Sevoflurane <small>(better smell)</small>	0.69	Rapid	2	Less potent
Desflurane <small>(Pungent smell)</small>	0.42 Low volatility	Poor induction due to its low volatile nature & Rapid recovery	6-7	Less potent
Nitrous oxide (Gas)	0.47 <small>(least soluble)</small>	Rapid	High MAC value >100	Least potent <small>Not used for long operations</small>

Pharmacological actions of inhalation anesthetics:

CNS



- ↓ metabolic rate (Gradual CNS depression).
- ↑ ICP (due to cerebral vasodilatation) thus **contraindicated in head injuries.**
- Dose-dependent EEG changes (Enflurane only).

CVS



- Hypotension.
- **Bradycardia EXCEPT: (Isoflurane, Desflurane).**
- Myocardial depression (prominent with Halothane, Enflurane).
- Sensitize heart to catecholamines (Halothane **only**, contraindicated in pheochromocytoma as it may cause tachycardia by making the heart sensitive to circulating catecholamines.)

Respiratory



- All respiratory depressants.
- Airway irritation (Desflurane, Enflurane) due to pungent odor.

Liver



- Decrease hepatic flow
- Hepatotoxicity (Halothane only) in **adults only**.



Uterus & skeletal muscle



- Uterine relaxation, but nitrous oxide has minimal relaxant effect (may delay labor).
- Skeletal muscle relaxants. (of variable degrees)

Inhalation anesthetics

Halothane is a weak analgesic and nitrous oxide is a potent analgesic and the rest are in between.

Anesthetic drugs	Properties 	Side effects 
Methoxyflurane (Not used in humans)	For veterinary (animal) use only	- Slow induction - Nephrotoxicity
Halothane 3Hs for side effects	- Potent anesthetic Note that analgesic ≠ anesthetic - Non irritant (pleasant odor) - Can be used in children	- Weak analgesic. - Slow induction and recovery due to high solubility - Hepatotoxicity in adults ONLY, not in children. - Malignant Hyperthermia (genetic predisposition → abnormal ryanodine receptor → huge Ca release in muscle cells → ↑ body temperature & acidosis + muscle rigidity). - Sensitization of Heart to catecholamines
Enflurane	Metabolized to fluoride (8%) Male's doctor mnemonics: F is the 3rd letter (unlike other drugs) which helps you remember that fluoride is much released with this drug thus nephrotoxic	- Airway irritation. - Pungent (less induction, Not for pediatrics). - CNS stimulation (Epilepsy-like seizure, abnormal EEG). Male's doctor mnemonics: E for Epilepsy - Contraindicated in patients with seizure disorders (because it causes EEG changes) - Contraindicated in patients with renal failures (release fluoride) - Involuntary movement.
Isoflurane	- Stable compound (2%), Low biotransformation (Less fluoride). - No nephrotoxicity - No hepatotoxicity. - Less Myocardial depression	-
*DOC Sevoflurane	- No airway irritation (in children better halothane) - Better smell, - Little effect on HR	-
Desflurane	- Less metabolized (0.05 %) - Low boiling point (special equipment)	- Pungent odor - Airway irritation
Nitrous oxide (Gas)	- Potent analgesics - Minimal CVS adverse effects (no myocardial depression or hypotension).	- Weak anesthetic (low potency, use combined). - Diffusion hypoxia (during recovery it rapidly leaves the CNS into the blood leading to its accumulation there) - Nausea & vomiting. - Inactivation of B12 (Chronic exposure) → Megaloblastic anemia, Congenital anomalies e.g. nurses working in operation rooms are at risk. - Contraindicated in pregnancy (minimal uterine relaxant).

Intravenous anesthetics

- NO need for special equipments.
- Rapid induction & recovery compared to inhalation EXCEPT benzodiazepines (the slowest IV)
- Injected slowly (due to its rapid induction) compared to inhalation.
- Recovery is due to redistribution from CNS. (where does it go? Majority is deposited in adipose tissue until it's metabolised by the liver while some goes to the liver directly.)
- **Analgesic activity:** Opioids, ketamine & Nitrous Oxide these 3 ONLY.
- **Amnesic action:** benzodiazepines & ketamine.
- Can be used alone in short operation & Outpatients anesthesia.
In long operations: Give IV for rapid induction, maintain with either Inhalation or IV.

Ultra short acting barbiturates, propofol and etomidate were also used as hypnotic agents.

Ultrashort acting barbiturates

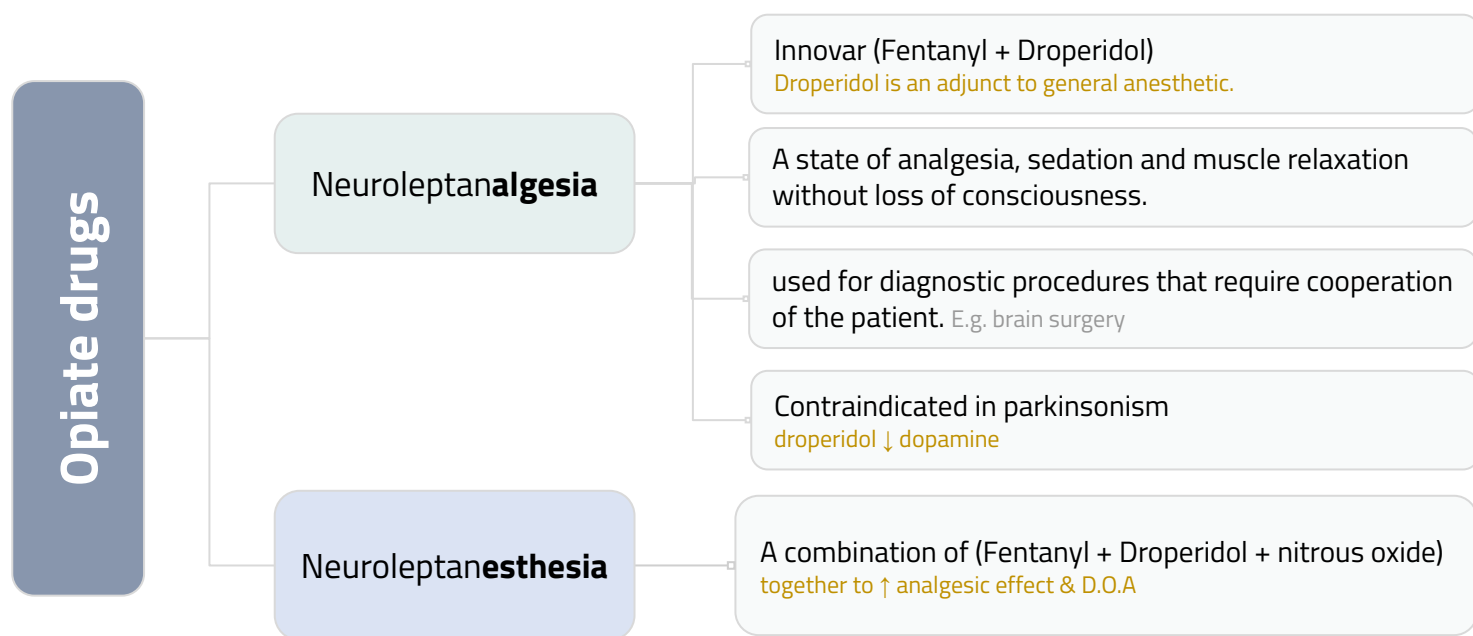
Drug	Thiopental & Methohexital (aldehydes)
Onset & D.O.A <small>Male dr: not important for IV</small>	Rapid onset (1 min) (high lipid solubility), Ultra short (15-20 min) D.O.A
Metabolism	Slowly by the liver, slow recovery → Hangover
Uses	<ul style="list-style-type: none"> - Potent anesthetic. - ↓ICP (used in head injury) unlike inhalation which was contraindicated - Induction in <u>major</u> surgery, then maintenance is done by other anesthetics. - Alone in <u>minor</u> surgery.
ADRs <small>pink: "add it to your slides"</small>	<ul style="list-style-type: none"> - CVS collapse & respiratory depression (Laryngospasm, bronchospasm) - Precipitate porphyria attack (Porphyria is a group of liver disorders in which substances called porphyrins build up in the body, negatively affecting the skin or nervous system). (symptoms: severe abdominal pain, numbness, anxiety & confusion) (↑porphyrin in blood by acting as liver microsomal enzyme inducers → ↑ enzyme involved in synthesis of porphyrin moiety → ↑ porphyrin moiety) - Hypersensitivity reaction.
Contraindication	- Severe hypotension (hypovolemic & shock patient) & COPD

Intravenous anesthetics

Drug	Etomidate Ultrashort acting hypnotic (<u>Non</u> Barbiturates)
Onset & D.O.A	Rapid onset & short D.O.A
Metabolism	<ul style="list-style-type: none"> - Rapidly in liver → less hangover - Fairly fast recovery
ADRs	<ul style="list-style-type: none"> - Minimal CVS & respiratory depressant effects. - Postoperative NV (nausea & vomiting). - Pain at injection site. - Involuntary movements/Excitatory effects during induction. ★ Adrenal/Adrenocortical suppression Male's doctor mnemonics: E for "Edrenal"
Drug	Propofol Hypnotic (<u>Non</u> Barbiturate)
Onset & D.O.A	Rapid onset & short D.O.A
Metabolism	<ul style="list-style-type: none"> - Rapidly in liver (10 times more than thiopental, Elimination $\frac{1}{2}$ = 30–60min). - Faster recovery than thiopental
Uses	<ul style="list-style-type: none"> - ↓ICP - Antiemetic action
ADRs	<ul style="list-style-type: none"> - Hypotension (↓peripheral vascular resistance), CVS & respiratory depression - Excitation (involuntary movements). - Pain at site of injection (not important). - Expensive (not important).
Group	Benzodiazepines (anxiolytic drugs)
Drug	Midazolam (most used in operations), Diazepam (mostly as preanesthetic), & Lorazepam
Onset, Induction & Recovery	Slow induction & recovery.
Uses	<ul style="list-style-type: none"> - No pain (no analgesic actions), have anxiolytic & amnesic action. - Induction of general anesthesia (Midazolam). - Alone in minor procedure (endoscopy, colonoscopy, bronchoscopy) - In balanced anesthesia (Midazolam).
ADRs	<ul style="list-style-type: none"> - Minimal CVS & respiratory depressant effects. - C.I: Respiratory depression/Patients in high doses

Intravenous anesthetics

Drug	Ketamine given IV, IM (can be used in children)
Onset & D.O.A	Rapid Onset, Short D.O.A
Uses <small>Imp note: All IV anesthetics are C.I in hypovolemia EXCEPT ketamine which is used because it ↑BP & CO.</small>	<ul style="list-style-type: none"> - Dissociative anesthesia (analgesic activity, amnesic action, immobility, complete separation from the surrounding environment). Not exactly a use, but a group of symptoms associated with Ketamine - Potent bronchodilator (asthmatics). - Used in (hypovolemic, shock & elderly <small>at risk of bradycardia during an operation, ketamine ↑ symp activity</small>) patients.
ADRs	<ul style="list-style-type: none"> - ↑ Central sympathetic activity (↑ BP & CO) - ↑ Plasma catecholamine levels (↑ ICP) <small>mnemonic: ketamine = catecholamine</small> - Post operative/Psychotomimetic effects: hallucination, vivid dreams, disorientation & illusions - Risk of hypertension and cerebral hemorrhage ↑ ICP (due to ↑ symp activity) - Post operative NV, salivation
Contraindication	CV diseases (hypertension, stroke) & Head injuries.
Group	Opiate drugs (morphine derivatives)
Drug	Fentanyl , Alfentanil, Sufentanil, Remifentanil <small>fentanyl derivatives, more potent.</small>
Onset & D.O.A	Rapid onset & short D.O.A
Uses <small>Alone or in combination</small>	<ul style="list-style-type: none"> - Potent analgesia. - Cardiac surgery (morphine + nitrous oxide)
ADRs	<ul style="list-style-type: none"> - Nausea & vomiting, Urinary Retention - ↑ICP - Prolongation of Labor & fetal distress - Respiratory depression, bronchospasm (wooden rigidity) - Hypotension
Contraindication	<ul style="list-style-type: none"> - Head injuries. (↑ ICP) - Pregnancy (respiratory depression) - Bronchial asthma, COPD (severe bronchospasm) - Hypovolemic shock (Large dose only)



Summary

Intravenous Anesthetics

Drug	Uses	ADRs	Contraindication
Barbiturates (Ultrashort acting) Thiopental & Methohexital	<ul style="list-style-type: none"> - Induction in major surgery and alone in minor surgery. - Potent anesthetic. - ↓ICP (used in head injury) 	<ul style="list-style-type: none"> - CVS collapse & respiratory depression (Laryngospasm, bronchospasm) - Precipitate porphyria attack - Hypersensitivity reaction. 	<ul style="list-style-type: none"> - Severe hypotension (hypovolemic & shock patient) - COPD
Etomidate Ultrashort acting hypnotic (Non Barbiturates)	-	<ul style="list-style-type: none"> - Minimal CVS & respiratory depressant effects. - Involuntary movements/Excitatory effects during induction. - Adrenal/Adrenocortical suppression 	-
Propofol Hypnotic (Non Barbiturate)	<ul style="list-style-type: none"> - ↓ICP - Antiemetic action 	<ul style="list-style-type: none"> - Hypotension (↓PVR), CVS & respiratory depression - Excitation (involuntary movements). 	-
Benzodiazepines Midazolam, Diazepam & Lorazepam	<ul style="list-style-type: none"> - No pain, have anxiolytic & amnesic action. - Induction of general anesthesia (Midazolam). - Alone in minor procedure (endoscopy) - In balanced anesthesia (Midazolam). 	<ul style="list-style-type: none"> - Minimal CVS & respiratory depressant effects. (Male Slides Only) 	Respiratory depression/Patients
Ketamine I.M (can be used in children)	<ul style="list-style-type: none"> - Dissociative anesthesia (analgesic activity, amnesic action, immobility, complete separation from the surrounding environment). - Potent bronchodilator (asthmatics). - Used in (hypovolemic, shock & elderly patients). 	<ul style="list-style-type: none"> - ↑ Central sympathetic activity (↑ BP & CO) - ↑ Plasma catecholamine levels (↑ ICP) - Post operative/Psychotomimetic effects: hallucination, vivid dreams, disorientation & illusions - Risk of hypertension and cerebral hemorrhage ↑ ICP - Post operative NV, salivation 	CV diseases (hypertension, stroke) & Head injuries.
Opiate drugs Fentanyl , Alfentanil, Sufentanil, Remifentanil	<ul style="list-style-type: none"> - Potent analgesia. - Cardiac surgery (morphine + nitrous oxide) 	<ul style="list-style-type: none"> - Nausea & vomiting, Urinary Retention - ↑ICP - Prolongation of Labor & fetal distress - Respiratory depression, bronchospasm (wooden rigidity) - Hypotension 	<ul style="list-style-type: none"> - Head injuries. - Pregnancy - Bronchial asthma, COPD - Hypovolemic shock (In Large dose only)

MCQs

Q1: Regarding levels of sedation, which one applies to loss of perception and sensation to painful stimuli?			
A- Anxiolysis	B-General anesthesia	C- Moderate sedation	D- Deep sedation
Q2: Regarding stages of sedation, which one does eye dilates in?			
A- Analgesia	B-Excitement	C-Surgical anesthesia	D-Comma & death
Q3: Which of the following determines the speed of recovery from intravenous anesthetics used for induction?			
A- Liver metabolism of the drug	B-Protein binding of the drug	C- Ionization of the drug	D- Redistribution of the drug from sites in the CNS
Q4: A 23-year-old patient with a history of severe postoperative nausea and vomiting is coming in for plastic surgery. Which anesthetic drug would be best to use for maintenance in this situation?			
A- Isolurane	B- Sevoflurane	C- Nitrous oxide	D- Propofol
Q5: Which one of the following is a potent intravenous anesthetic and analgesic?			
A- Propofol	B- Midazolam	C- Ketamine	D- Fentanyl
Q6: Inhaled anesthetics and intravenous agents having general anesthetic properties:			
A- Directly activate GABA A receptors	B- Facilitate GABA action but have no direct action on GABA A receptors	C- Reduce the excitatory glutamatergic neurotransmission	D- Increase the duration of opening of nicotine-activated potassium channels
Q7: Which of the following inhalants lacks sufficient potency to produce surgical anesthesia by itself and therefore is commonly used with another inhaled or intravenous anesthetic?			
A- Halothane	B- Sevoflurane	C- Nitrous Oxide	D- Desflurane
Q8: Indicate the inhaled anesthetic, which causes the airway irritation			
A- Nitrous Oxide	B- Sevoflurane	C- Halothane	D- Desflurane
Q9 Indicate the inhaled anesthetic, which should be avoided in patients with a history of seizure disorders			
A- Enflurane	B- Nitrous Oxide	C- Sevoflurane	D- Desflurane

1	2	3	4	5	6	7	8	9
B	B	D	D	C	A	C	D	A

SAQ

Q1) Mention 3 drugs that can be used as Preanesthetic medications

Q2) Explain the MOA of general anesthetics.

Q3) Dissociative anesthesia is commonly seen with which drug? Explain how it presents.

Q4) A patient doesn't seem to fully respond to anesthetics. What can be used as a helpful adjunct? Mention its uses and some examples.

Q5) A patient came to the ED with head trauma which he has to undergo surgery for, mention 2 I.V anesthetics preferred for this case.

Q6) Mention 3 ADRs of Halothane.

A1) [Slide 4](#)

A2) Enhance the action of GABA and glycine on receptors thus ↓ neuronal excitability.

A3) Ketamine, Dissociative anesthesia: (analgesic activity, amnesic action, immobility, complete separation from the surrounding environment).

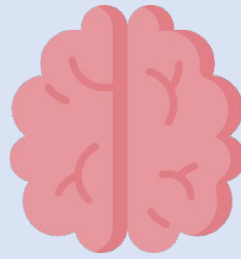
A4) Neuromuscular blockers. Facilitate intubation & Suppress muscle tone. E.g. Succinylcholine, vecuronium & atracurium

A5) Thiopental, Propofol

A6) Hepatotoxicity, Malignant Hyperthermia, Sensitization of Heart to catecholamines



Feedback Form



Neuropsychiatry Block

Pharmacology Team 439

Leaders

Banan AlQady

Ghada AlOthman

Khaled AlSubaie

Organizers

- Duaa Alhumoudi
- Ghada Aljedaie
- Haya Alanazi
- Mais Alajami
- Norah Alasheikh
- Nouf Alsubaie
- Sadem Alzayed
- Shayma Alghanoum
- Tarfa Alsharidi

Note Takers

- Ghadah Alsuwailem
- Homoud Algadheb
- Omar Alhalabi
- Mishal Althunayan
- Yasmine Alqarni

Revisers

- Omar Alhalabi
- Mayasem Alhazmi
- Mishal Althunayan

Members

- Abdulaziz Alderaywsh
- Abdulaziz Alghuligah
- Abdulrahman Almebki
- Abdulrhman Alsuhaibany
- Abdurahman Addweesh
- Albandari Alanazi
- Aljoharah Albnyan
- Aljoud Algazlan
- Dana Naibulharam
- Fatimah Binmeather

- Feras Alqaidi
- Lama Alahmadi
- Maha Alanazi
- Manal Altwaim
- Mayasem Alhazmi
- Mona Alomiriny
- Norah Almasaad
- Noura Bamarei
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- Sarah Alqahtani
- Shahad Almezel
- Shatha Aldhohair
- Teif Almutiri
- Yara Alasmari