

General Anaesthetics

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE



Objectives



Define anesthesia and balanced anesthesia



Identify the main classification of general anesthetics



Describe the mechanism of action for general anesthetics



Identify pharmacokinetics and major adverse effects of general anesthetics

Introduction



Types of Anesthesia:

General Anesthesia

Drugs used to induce **loss of pain sensation**, loss of consciousness, skeletal muscle relaxation, analgesia, amnesia and inhibitions of undesirable reflexes
e.g. Bradycardia. "It's a definition of an ideal general anesthetic"

Local Anesthesia

Cocaine derivatives e.g. Lidocaine



Characters of an ideal anesthetic drug:

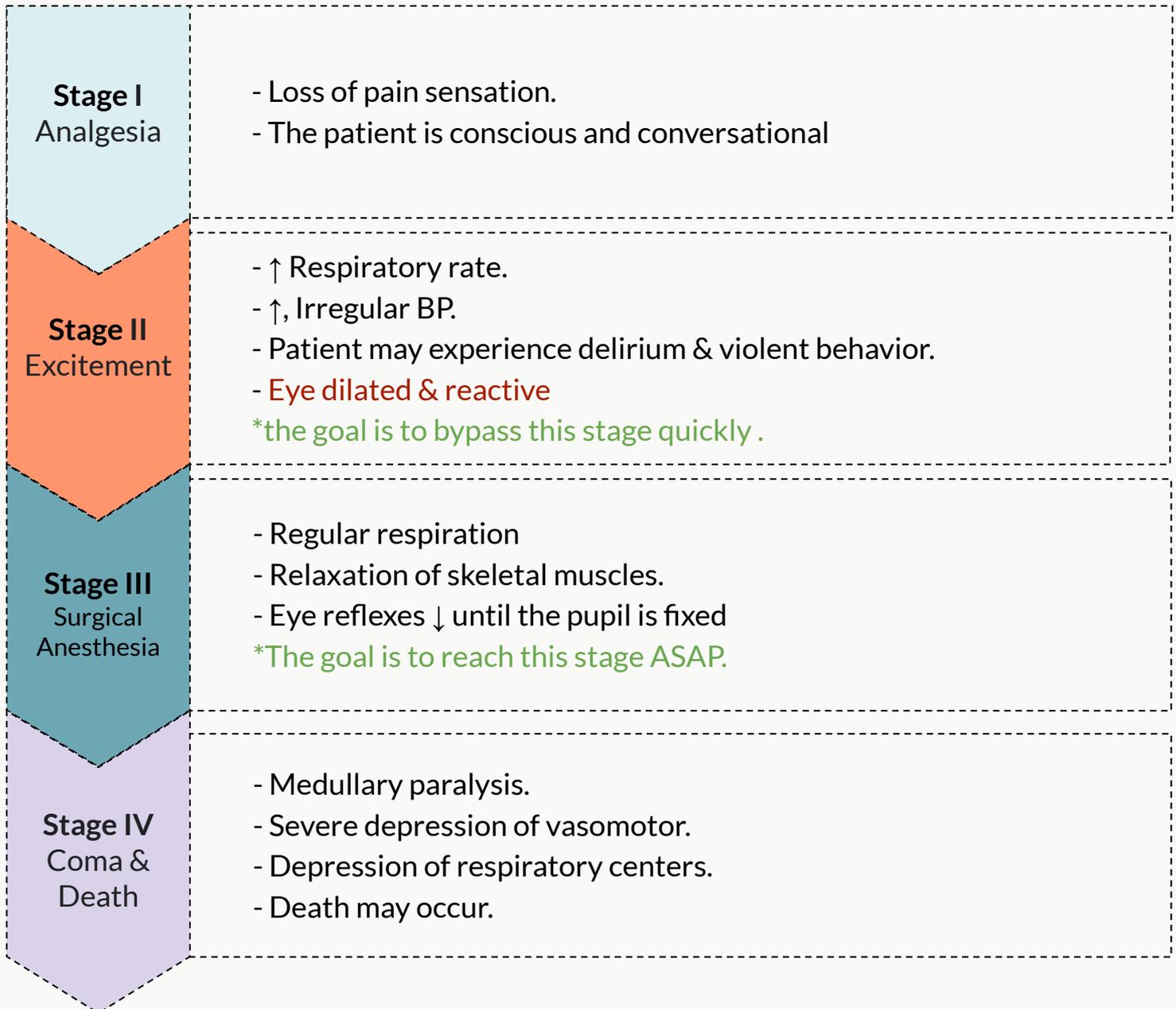
- 1 Smooth and rapid induction **Able to bypass the first two stages of anesthesia and reach stage III rapidly**
- 2 Rapid Recovery (**regain consciousness**)
- 3 Wide safety margin
- 4 Minimal side effects

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 (**sometimes, orally**)

Stages of Anesthesia

progressive CNS depression



	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		No response to skin incision
	Plane 2				Pupillary light		
	Plane 3						
	Plane 4						
STAGE IV: IMMINENT DEATH	Apnea					Flaccid	

Advantages of pre-Anesthetic Medications

- Calm the patient & relieve pain e.g: diazepam
- Protect against undesirable effects of the subsequently administered anesthetics or the surgical procedure (anticholinergics drugs are given to prevent the activation of parasympathetic system and protect against expected bradycardia)
- Facilitate smooth induction of anaesthesia. (Bypass stage 2) e.g: thiopental
- Lower the dose of anaesthetic required. CNS depressant drugs , e.g: diazepam

Pre-Anesthetic Medications (adjuncts to general anesthetics)

Drugs	Examples	Uses
Opiates	Morphine	Induce analgesia & open heart surgery
Anticholinergics	Hyoscine	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.
Sedatives & anxiolytics	Diazepam	Relieve anxiety
Antihistamines	Diphenhydramine	Postoperative Allergic reactions
Antiemetics	Metoclopramide & prochlorperazine	Post or pre surgical nausea & vomiting.
H2-receptor blockers	Ranitidine	Postoperative to reduce gastric acidity
Barbiturates Can be used alone I.V	Thiopental	Smooth induction

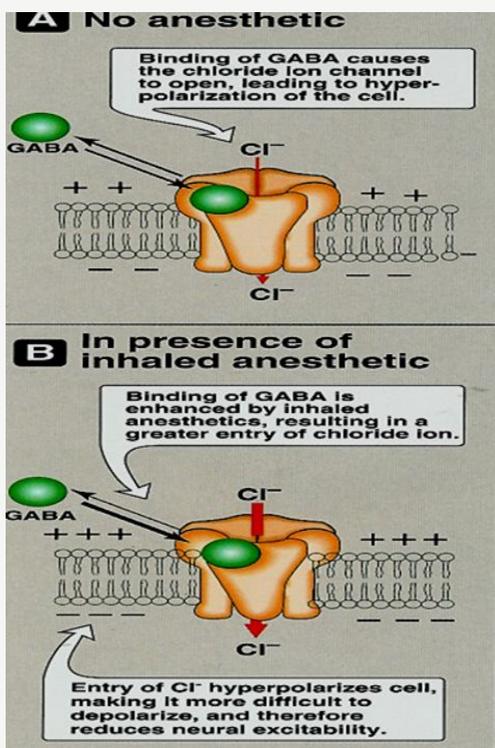
Adjuncts to general anesthesia

Drugs	Examples	Uses
Neuromuscular blockers Skeletal Muscle Relaxant	<ul style="list-style-type: none"> ○ Succinylcholine ○ vecuronium ○ atracurium 	<ul style="list-style-type: none"> ○ Facilitate intubation ○ Suppress muscle tone are given if the anesthetic drug doesn't cause skeletal muscle relaxation

Overview of General Anesthetics

Inhalation	Intravenous Used for induction
1. Gas	1. Slower-acting
<ul style="list-style-type: none"> ○ Nitrous oxide ○ xenon not used anymore 	<ul style="list-style-type: none"> ○ Dissociative anesthesia: <ul style="list-style-type: none"> ○ Ketamine ○ Opioid analgesia: <ul style="list-style-type: none"> ○ Fentanyl ○ Benzodiazepines (Preanesthetics): <ul style="list-style-type: none"> ○ Diazepam ○ Lorazepam ○ Midazolam
2. Volatile Liquids	2. Inducing Agent
<ul style="list-style-type: none"> ○ Methoxyflurane ○ Halothane ○ Isoflurane ○ Enflurane ○ Sevoflurane ○ Desflurane ○ Ether not used 	<ul style="list-style-type: none"> ○ Barbiturates (Ultra short acting): Thiopental methohexital ○ Propofol ○ Etomidate ○ Droperidol (not imp)

★ MOA of General anesthetics



Regardless the drug type or route of administration they have the same MOA:

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

★ Blocking NMDA receptors (**Ketamine**):

- Reduce Ca²⁺ influx
- Reduce neural excitability

- GABA + Glycine → inhibitory NTs → work on Cl⁻/K⁺
- Glutamate → excitatory NT → work on Ca⁺⁺

Inhalation Anesthetics

Terminology of Anesthesia	
Induction	Time elapsed between onset of administration of anesthetic and development of effective surgical anesthesia
Maintenance	Time during which the patient is surgically anesthetized
Recovery	The time from discontinuation of anesthetic drug until consciousness is regained



P.K of Inhalation Anesthetics

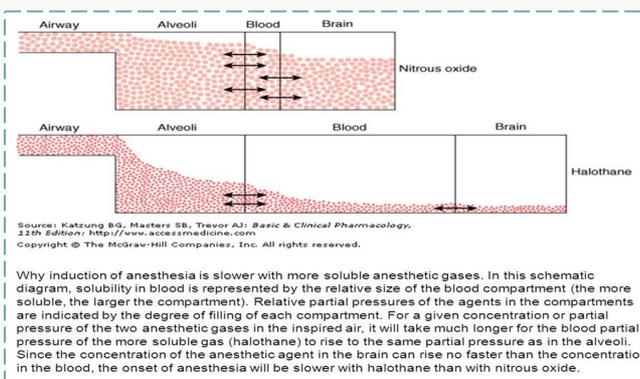
© Pharmacokinetics of Inhalation Anesthetics include:

1- Rate of induction

2- Depth of anesthesia and recovery

Factors controlling induction & recovery	
Direct	1. Anesthetic concentration 2. Rate & depth of ventilation
Inverse	3. Blood solubility (Blood: gas partition coefficient)

© Solubility & Induction of Anesthesia



(Inverse relation shown in next slide)

© Minimum alveolar concentration (MAC):

- Is the concentration of inhalation anesthetic that produce immobility in **50%** patients in response to surgical operation.
- The lower the MAC value the more potent the drug (Inverse relation shown in next slide)
- MAC value \uparrow with CNS stimulants & \downarrow with CNS depressants



P.K of Inhalation Anesthetics. cont...



NOTE:

The following table shows the **inverse** relationship between:

1. **Solubility & Induction:** ↑ blood Solubility, ↓ induction (as you go up)
2. **MAC value & Potency:** ↑ MAC value , ↓ potency (as you go down)

Drugs		Inverse Relationship		Inverse Relationship	
		Solubility	Induction & recovery	MAC value	Potency
Volatile Liquids	Methoxyflurane - Toxic, not used anymore-	12	Slow	0.16 Low MAC value	Most potent
	Halothane Pleasant smell, used in children	2.3	Slow	0.75	Potent
	Enflurane Pungent smell → airway irritation	1.8	Medium	1.7	Less potent
	Isoflurane	1.4	Medium / Rapid	1.4	Less potent
	Sevoflurane better smell, used in children	0.69	Rapid	2	Less potent
	Desflurane Pungent smell → airway irritation	0.42 Low volatility	- Rapid induction - Rapid recovery	6-7	Less potent
Gas	Nitrous Oxide	0.47 (least soluble)	Rapid	>100 High MAC value	Least potent

"Numbers are not important"



★ **Methoxyflurane:**

- **Highest** solubility, **slowest** induction
- **Least** MAC value, **most** potent

★ **Nitrous Oxide:**

- **Lowest** solubility, **fastest** induction
- **Highest** MAC value, **least** potent

Pharmacological Actions of Inhalation Anesthetics

CNS	<ul style="list-style-type: none">◦ ↓ Metabolic rate◦ ↑ ICP (due to cerebral vasodilatation) → ★C.I in head injuries (Inhalator)◦ Enflurane: Dose dependent EEG changes
CVS	<ul style="list-style-type: none">◦ Hypotension◦ Bradycardia, EXCEPT: Isoflurane & Desflurane◦ Halothane & Enflurane: myocardial depression◦ Halothane: sensitize heart to catecholamines
Respiratory	<ul style="list-style-type: none">◦ All respiratory depressants (bronchodilation) EXCEPT: Desflurane (★C.I in patient with asthma)◦ Desflurane & Enflurane: airway irritation
Uterus & Skeletal Muscles	<ul style="list-style-type: none">◦ Skeletal muscle relaxants◦ Uterine relaxation [nitrous oxide has minimal relaxant effect (may delay labor)]

Side Effects of Inhalation Anesthetics

© **Malignant Hyperthermia**: is a severe reaction that is caused a genetic condition of skeletal muscle metabolism triggered by inhalation anesthetics.

★ **Treatment: Dantrolene**

Mutations in the RYR1 gene

↓
Altered Ca²⁺ release channel protein (RYR1)
(eg. substitution of Cys for Arg⁶¹⁵)

↓
Mutated channel opens more easily and stays open longer, thus flooding the cytosol with Ca²⁺

↓
High intracellular levels of Ca²⁺ stimulate sustained muscle contraction (rigidity); high Ca²⁺ also stimulate breakdown of glycogen, glycolysis, and aerobic metabolism (resulting in excessive production of heat)

Inhalation Anesthetics

Anesthetic drugs	Properties	Side effects
Methoxyflurane prodrug + very toxic	For veterinary use only	<ul style="list-style-type: none"> ◦ Slow induction ◦ Nephrotoxicity (it is high in fluoride)
<u>H</u>alothane 3Hs for side effects	<ul style="list-style-type: none"> ◦ Potent anesthetic, Weak analgesic. ◦ Non irritant (pleasant odor) ◦ Can be used in children 	<ul style="list-style-type: none"> ◦ Slow induction and recovery due to high solubility ◦ Hepatotoxicity in adults ONLY ◦ Malignant Hyperthermia (genetic predisposition → abnormal ryanodine receptor → huge Ca release in muscle cells → ↑ body temperature & acidosis + muscle rigidity). ◦ Sensitization of Hear to catecholamines
<u>E</u>nflurane	Metabolized to fluoride (8%) therefore is nephrotoxic	<ul style="list-style-type: none"> ◦ Airway irritation (due to Pungent Smell) ◦ Not for pediatrics ◦ less induction ◦ CNS stimulation : <ul style="list-style-type: none"> - ★ ★ (Epilepsy-like seizure, abnormal EEG). - Contraindicated in patients with seizure disorders ◦ Contraindicated in patients with renal failures (release fluoride) ◦ Changes in ECG: prolongation of QT & cardiac depression
Isoflurane	<ul style="list-style-type: none"> ◦ Stable compound (2%), Low biotransformation (Less fluoride). ◦ No nephrotoxicity ◦ No hepatotoxicity. 	-
Sevoflurane	<ul style="list-style-type: none"> ◦ Better smell, No airway irritation (used for children) ◦ Little effect on HR 	-
Desflurane	<ul style="list-style-type: none"> ◦ Less metabolized (0.05 %) ◦ Low boiling point special equipment 	<ul style="list-style-type: none"> ◦ Pungent odor ◦ Airway irritation ★ (C.I in patient with asthma)
Nitrous oxide (Gas)	<ul style="list-style-type: none"> ◦ Potent analgesics ◦ Minimal CVS adverse effects (no myocardial depression or hypotension) 	<ul style="list-style-type: none"> ◦ Weak anesthetic (low potency, so combined). ◦ Diffusion hypoxia ◦ Nausea & vomiting. ◦ Inactivation of B12 → Megaloblastic anemia, Congenital anomalies. e.g: nurses working in operation rooms are at risk . ◦ Contraindicated in pregnancy (uterine relaxant, labor)

Intravenous Anesthetics

- ⊘ Injected slowly, NO need for special equipments.
- ⊘ Rapid induction & recovery compared to inhaled anesthetics **except benzodiazepines**
- ⊘ Can be used alone in short operation & Outpatients anesthesia.
- ⊘ Recovery is due to redistribution from CNS.
- ⊘ **Analgesic activity:** Opioids, Ketamines
- ⊘ **Amnesic action:** Benzodiazepines, Ketamines

	Ultrashort acting barbiturates	(Non Barbiturates)	
Drug	Thiopental & Methohexital (aldehydes).	Etomidate Ultrashort acting hypnotic	Propofol (Hypnotic)
Onset & D.O.A	<ul style="list-style-type: none"> ◦ High lipid solubility ◦ Rapid onset (1 min) ◦ Ultra short D.O.A (15-20 min) 	Rapid onset & short D.O.A	Rapid onset & short D.O.A
Metabolism	<ul style="list-style-type: none"> ★ Slowly metabolized by the liver, slow recovery → Hangover 	Rapidly in liver, fairly fast recovery → less hangover	<ul style="list-style-type: none"> ◦ Rapidly metabolized in liver (10 times Elimination $\frac{1}{2}$ = 30-60min). ◦ Faster recovery than thiopental.
Uses	<ul style="list-style-type: none"> ◦ Potent anesthetic. ★ CNS: ↓ICP (used in head injury) unlike inhalation anesthetics which ↑ ICP ◦ Induction in major surgery and Alone in minor surgery. 	-	<ul style="list-style-type: none"> ◦ ↓ICP ◦ Antiemetic action
ADRs	<ul style="list-style-type: none"> ◦ CVS collapse & respiratory depression (Laryngospasm, bronchospasm) ◦ Precipitate porphyria attack: <ul style="list-style-type: none"> - symptoms: severe abdominal pain, numbness, anxiety & confusion - severe hypotension (hypovolemic & shock patient) - ↑ porphyrin in blood by acting as liver microsomal enzyme inducers → ↑ enzyme involved in synthesis of porphyrin - Porphyria is a group of liver disorders in which substances called porphyrins build up in the body, negatively affecting the skin or nervous system ◦ Hypersensitivity reaction ◦ Chronic obstructive lung disease ◦ Local tissue necrosis & ulceration if injected SC or IM (highly alkaline) 	<ul style="list-style-type: none"> ★ Adrenal/ Adrenocortical suppression ◦ Minimal CVS & respiratory depressant effects. ◦ Postoperative NV (nausea & vomiting). ◦ Pain at injection site. ◦ Involuntary movements/Excitatory effects during induction. 	<ul style="list-style-type: none"> ◦ CVS and respiratory depression ◦ Hypotension (↓peripheral vascular resistance) ◦ Excitation (involuntary movements). ◦ Pain at site of injection ◦ Expensive ◦ Propofol infusion syndrome

Intravenous Anesthetics

Benzodiazepines (anxiolytic drugs)

Drug	<ul style="list-style-type: none"> ◦ Midazolam ◦ Diazepam (mostly as preanesthetic) ◦ Lorazepam
Induction & Recovery	<ul style="list-style-type: none"> ◦ Slow induction & recovery. *Only IV drug of slow induction ◦ Midazolam have slower onset than other agents
Uses	<ul style="list-style-type: none"> ◦ No pain (analgesic action) , have anxiolytic & amnesic action. ◦ Alone in minor procedure (endoscopy) ◦ Induction of general anesthesia ◦ Midazolam: In balanced anesthesia & has amnesic effect (GABA effect)
ADRs	Cause respiratory depression
C.I of Midazolam	Minimal CVS & respiratory depressant effects, contraindicated in Respiratory Patients

Drug: Ketamine (given IV, IM (can be used in children))

Onset and D.O.A	Slow onset, Short D.O.A
Actions	<ul style="list-style-type: none"> ◦ Dissociative anesthesia: analgesic activity, amnesic action, immobility, complete separation from the surrounding environment ◦ ↑Central sympathetic activity (★↑BP & CO): Used in hypovolemic shock & elderly patients ★-Potent bronchodilator (asthmatics) ◦ ↑Plasma catecholamine levels (↑ ICP): elderly patients : catecholamines will protect them from postoperative bradycardia
ADRs	<ul style="list-style-type: none"> ◦ Post operative effects (psychotomimetic effects following recovery): hallucination, vivid dreams, disorientation & illusions ◦ Risk of hypertension due to : increase of sympathetic activity ◦ cerebral hemorrhage ↑ ICP ◦ Post operative NV, salivation
Contraindication	CV diseases (hypertension, stroke) & Head injuries.

⚠ All IV anesthetics are # in hypovolemia EXCEPT ketamine (↑BP & CO)

Intravenous Anesthetics

Opiate drugs : Fentanyl, Alfentanil

Onset & D.O.A	Rapid onset & short D.O.A	
Uses	<ul style="list-style-type: none"> ★ Potent analgesia. ★ Cardiac surgery (morphine + nitrous oxide) 	
	<p>Neuroleptanalgesia Innovar (Fentanyl + Droperidol):</p> <ul style="list-style-type: none"> ◦ A state of analgesia, sedation and muscle relaxation without loss of consciousness. ◦ used for diagnostic procedures that require cooperation of the patient. ◦ Contraindicated in parkinson's. 	<p>Neuroleptanesthesia (loss of consciousness) (Fentanyl + Droperidol + nitrous oxide). A combination of drugs to increase the analgesic effect</p>
ADRs	<ul style="list-style-type: none"> ◦ Nausea & vomiting, Urinary Retention ◦ ↑ICP, Hypotension ◦ Prolongation of Labor & fetal distress ◦ Respiratory depression, bronchospasm (wooden rigidity) 	
C.I	<ul style="list-style-type: none"> ◦ Head injuries. (↑ ICP) ◦ Pregnancy (respiratory depression) ◦ Bronchial asthma, COPD (severe bronchospasm) ◦ Hypovolemic shock (large dose only) (hypotension) 	

Induction drugs effects on CVS system

Drug	Systemic BP	Heart rate
Propofol	↓	↓
Etomidate	No change or slight ↓	No change
★ Ketamine	↑	↑

Summary

Intravenous Anesthetics			
Drug	Uses	ADRs	C.I
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) (NonBarbiturate)	<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"> - Cause respiratory depression 	<ul style="list-style-type: none"> - Respiratory depression/Patients - Minimal CVS & respiratory depressant effects.
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"> - 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)



MCQ

1.Regarding stages of sedation, which one does eye dilates in?

- | | | | |
|-------------|--------------|-----------------------|-----------------|
| A.Analgesia | B.Excitement | C.Surgical anesthesia | D.Comma & death |
|-------------|--------------|-----------------------|-----------------|

2.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.Isoflurane | B.Sevoflurane | C.Nitrous oxide | D.Propofol |
|--------------|---------------|-----------------|------------|

3.Which one of the following is a potent intravenous anesthetic and analgesic?

- | | | | |
|------------|-------------|------------|-------------|
| A.Propofol | B.Midazolam | C.Ketamine | D.Etomidate |
|------------|-------------|------------|-------------|

4.Indicate the inhaled anesthetic, which causes the airway irritation

- | | | | |
|-----------------|---------------|-------------|--------------|
| A.Nitrous Oxide | B.Sevoflurane | C.Halothane | D.Desflurane |
|-----------------|---------------|-------------|--------------|

5.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 |
|-------------|-----------------|---------------|--------------|

6.A 30 years old patient come to the ER and he has head injury from car accident & it was prepared to have surgery, which of the following anesthesia should be used?

- | | | | |
|-----------------|-------------|--------------|--------------|
| A.Nitrous Oxide | B.Enflurane | C.Desflurane | D.Thiopental |
|-----------------|-------------|--------------|--------------|



SAQ

01

★ Explain the MOA of general anesthetics.

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

02

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

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

03

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

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

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