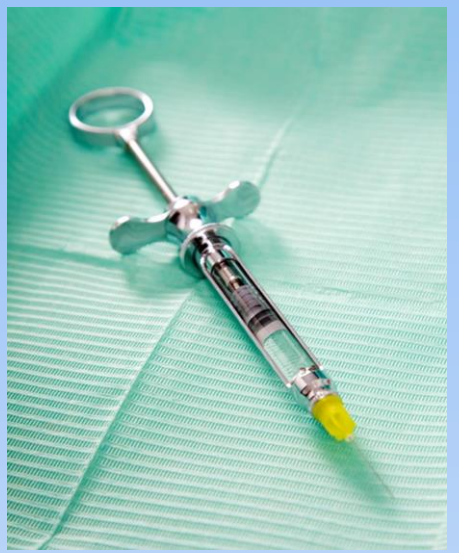

GENERAL ANESTHETICS

Prof. Hanan Hagar
Professor of Pharmacology
College of Medicine
King Saud University

Introduction

Drugs used to induce loss of pain sensation, loss of consciousness, skeletal muscle relaxation, analgesia, amnesia and inhibitions of undesirable autonomic reflexes.

Types of Anesthesia

- **General anesthesia**
- **Local anesthesia**

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STAGES OF ANESTHESIA

- **Stage I (analgesia)**

-Loss of pain sensation.

-The patient is conscious and conversational.

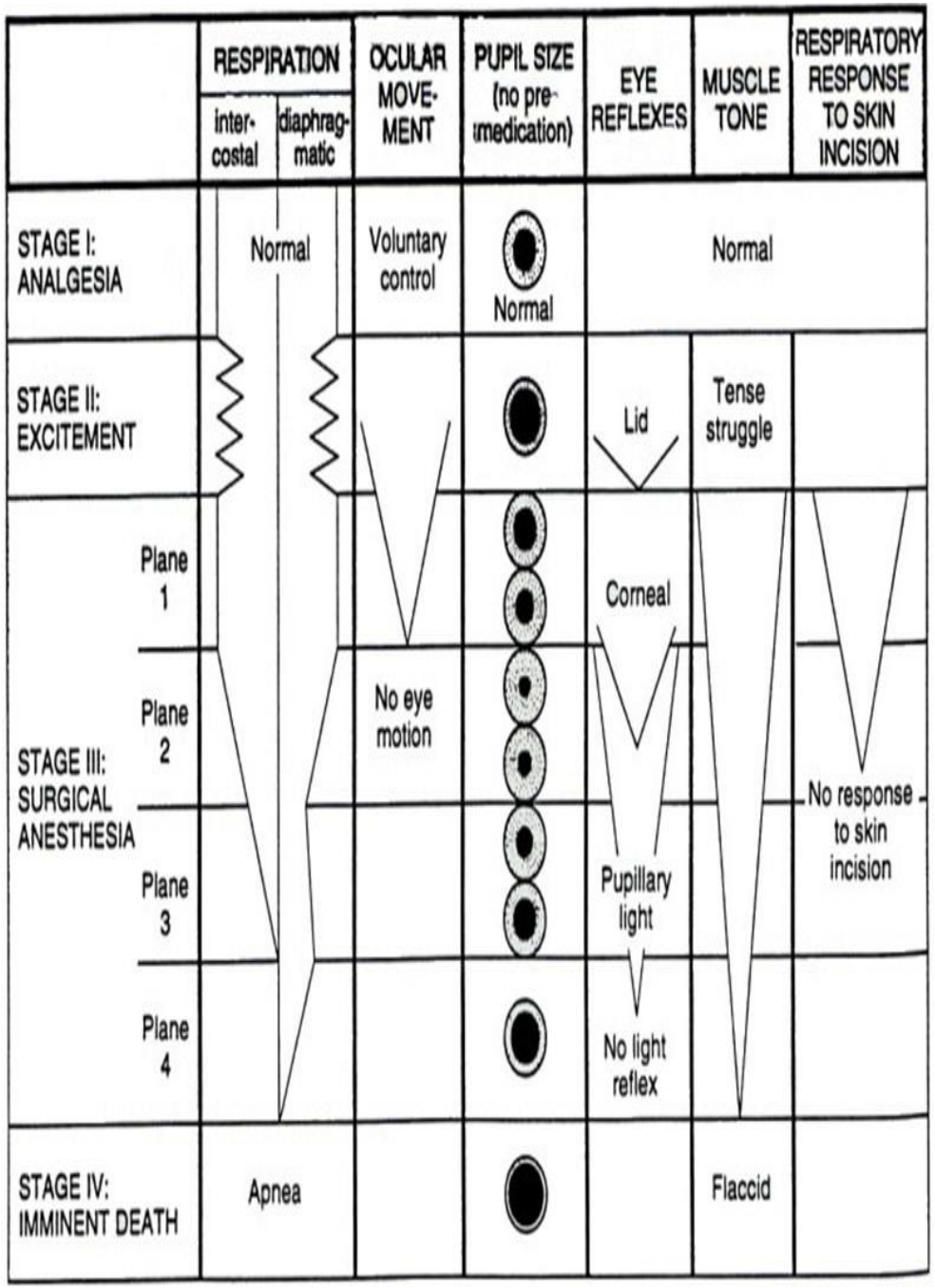
- **Stage II (Excitement)**

-Increased respiratory rate.

-Increased, irregular blood pressure.

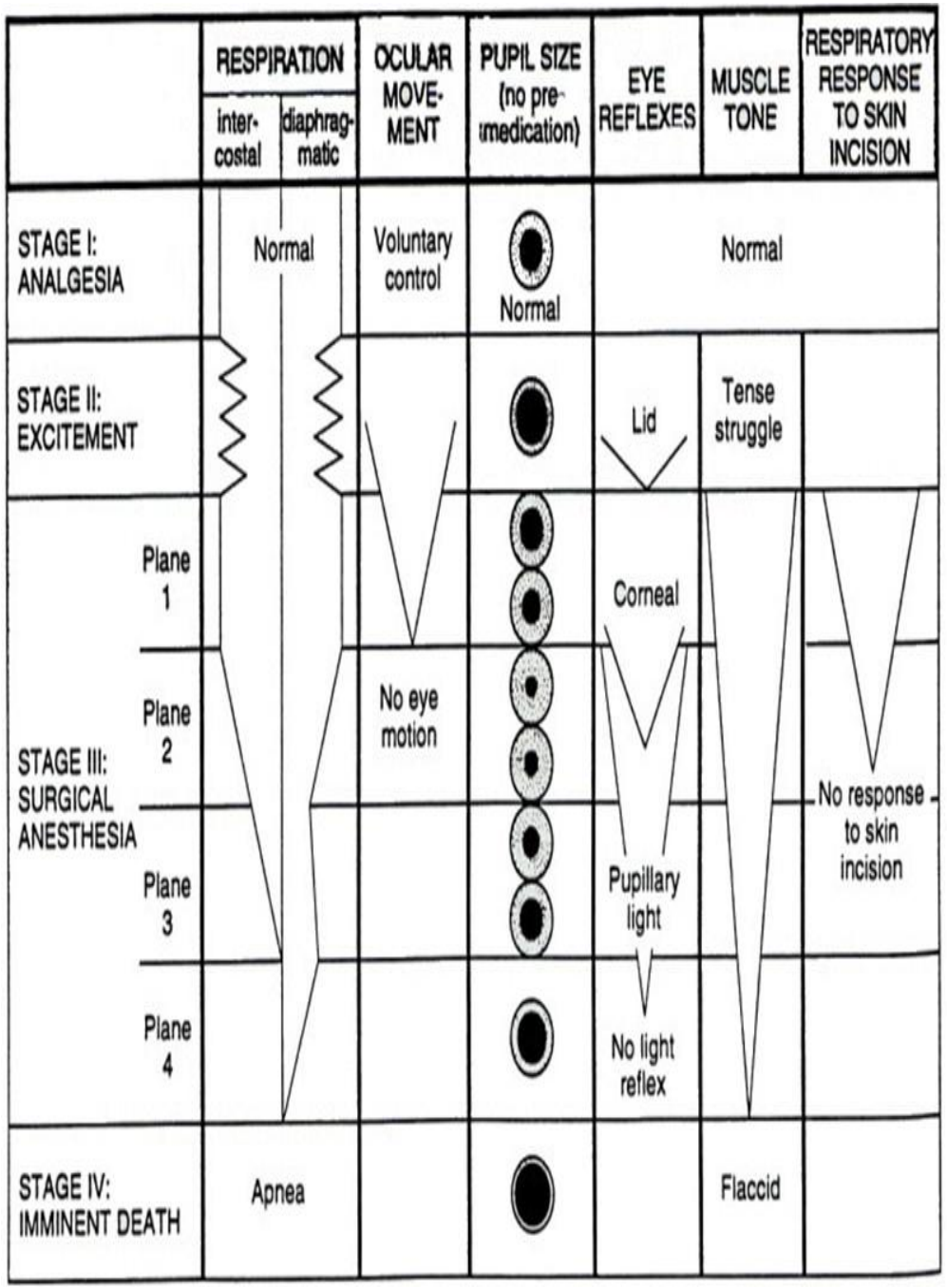
-Patient may experience delirium & violent behavior.

-Eye dilated & reactive.



STAGES OF ANESTHESIA

- **Stage III (Surgical anesthesia)**
  - **Regular respiration & relaxation of Sk. muscles.**
  - **Eye reflexes decrease until the pupil is fixed.**
- **Stage IV (coma and death)**
  - **Medullary paralysis.**
  - **Severe depression of vasomotor**
  - **Depression of respiratory centers.**
  - **Death may occur.**



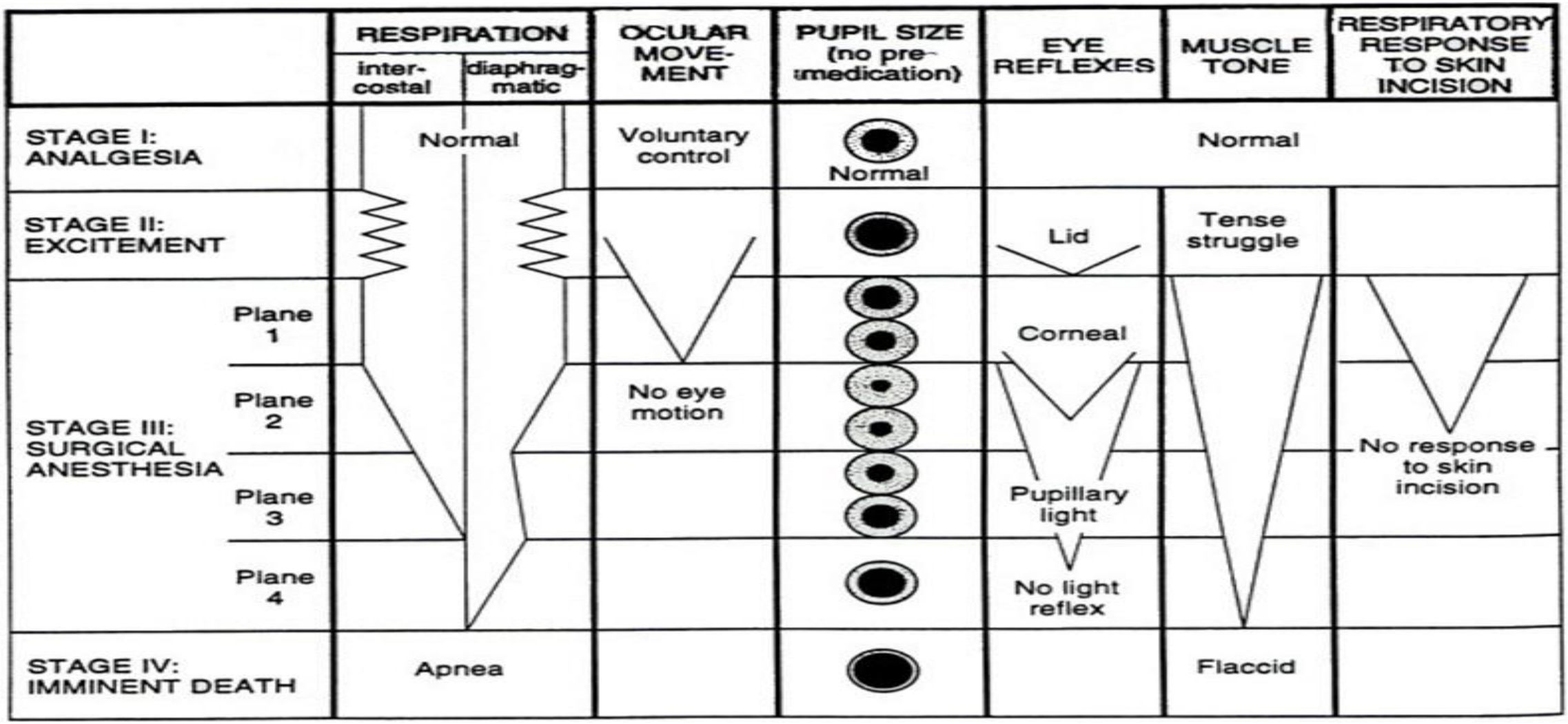
STAGES OF ANESTHESIA

The III stage is divided into 4 planes.

The order of depression in the CNS is:

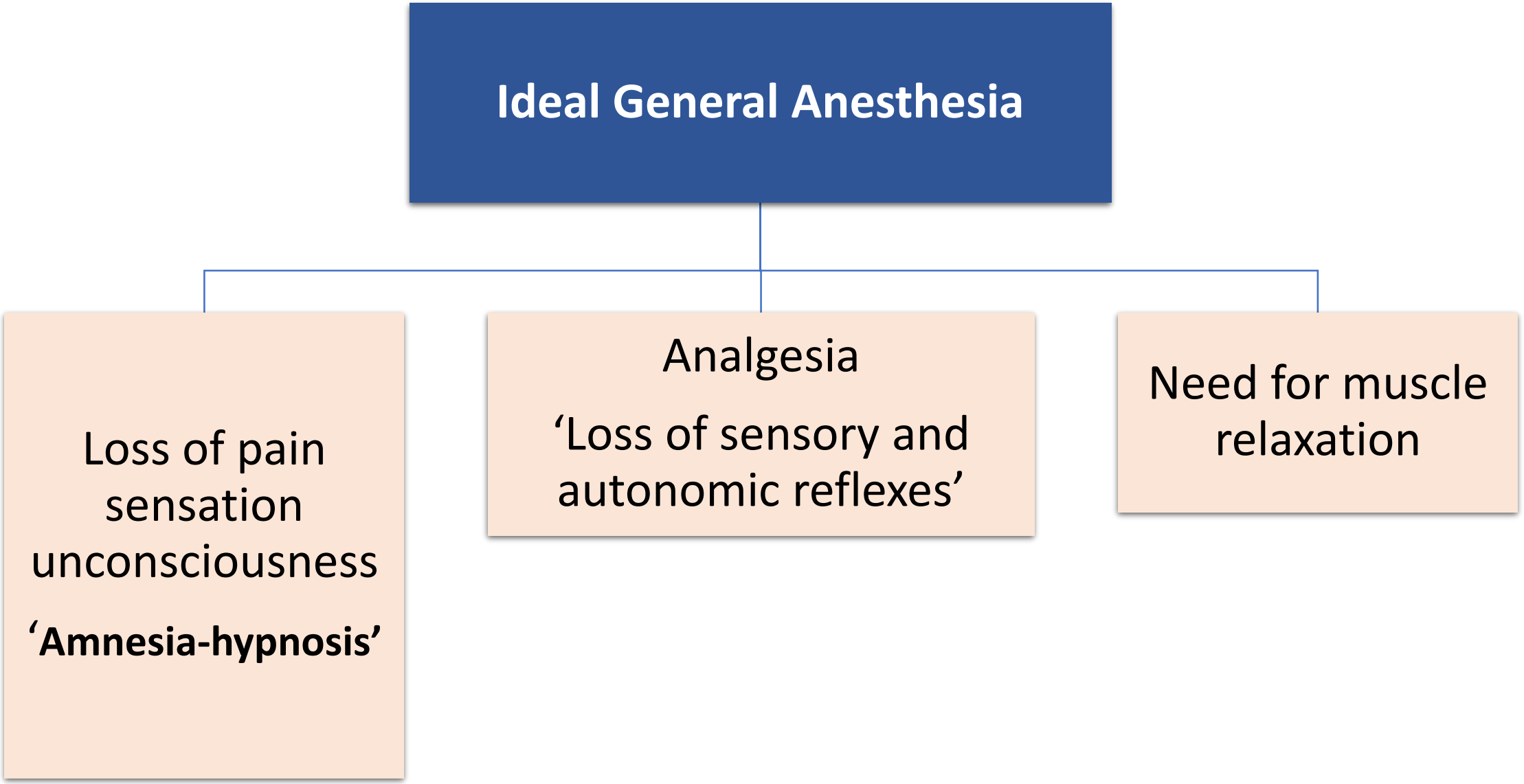
1. Cortical centers
2. Basal ganglia
3. Spinal cord
4. Medulla

STAGES OF ANESTHESIA



CHARACTER S OF AN IDEAL ANESTHETIC DRUG

1. **Smooth and rapid induction.**
2. **Rapid recovery.**
3. **Wide safety margin.**
4. **Minimal side effects.**


Ideal General Anesthesia
Loss of pain sensation unconsciousness
'Amnesia-hypnosis'
Analgesia
'Loss of sensory and autonomic reflexes'
Need for muscle relaxation

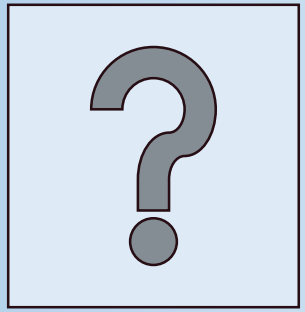
BALANCED ANAESTHESIA

Is the use of more than one drug in combination to fulfil the patient needs.

Beneficial effects

Adverse effects

HOW WE CAN OBTAIN BALANCED ANESTHESIA



Balanced anesthesia is achieved by a combination of I.V and inhaled anesthesia and Pre-anaesthetic medications

PRE-ANESTHETIC MEDICATION

- **Calm the patient, relieve pain**
- **Protect against undesirable effects of the subsequently administered anesthetics or the surgical procedure.**
- **Facilitate smooth induction of anaesthesia**
- **Lowered the dose of anaesthetic required**

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PRE - ANAESTHETIC MEDICATION

- **Opiates:** induce analgesia e.g. morphine
- **Anticholinergics:** prevent secretion of fluids into the respiratory tract e.g. hyoscine
- **Sedatives & anxiolytics:** relieve anxiety. e.g. diazepam
- **Antihistaminics:** allergic reactions. e.g. diphenhydramine
- **Antiemetics :** post surgical N&V. e.g. metoclopramide, prochlorperazine
- **H2-receptor blockers:** reduce gastric acidity e.g. ranitidine
- **Thiopental:** smooth induction

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ADJUNCTS TO GENERAL ANAESTHETICS

- **Pre-anesthetic medication.**
- **Neuromuscular blocking agents**
  - e.g. succinylcholine, vecuronium, atracurium
  - Facilitate intubation
  - Suppress muscle tone.

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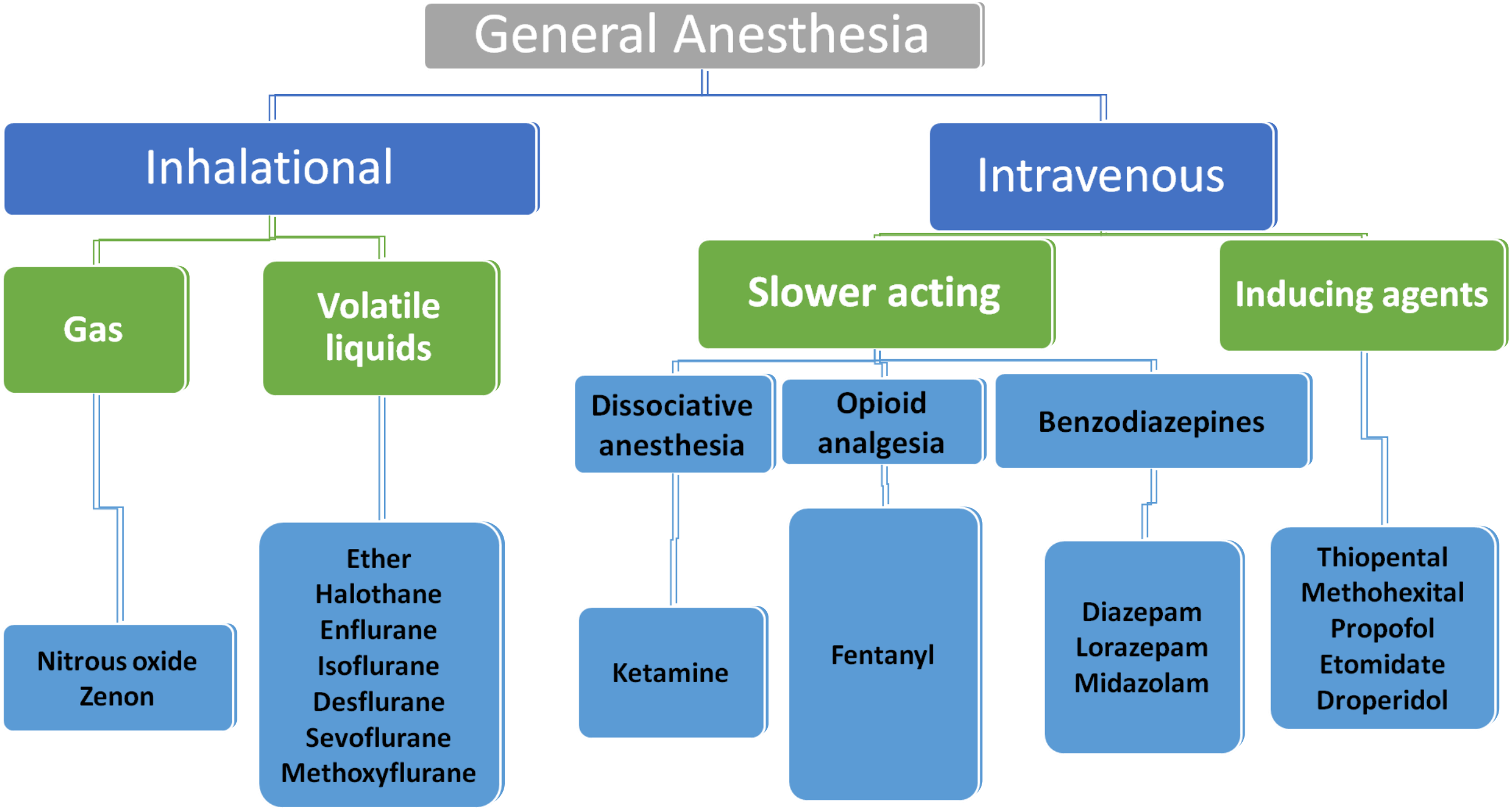
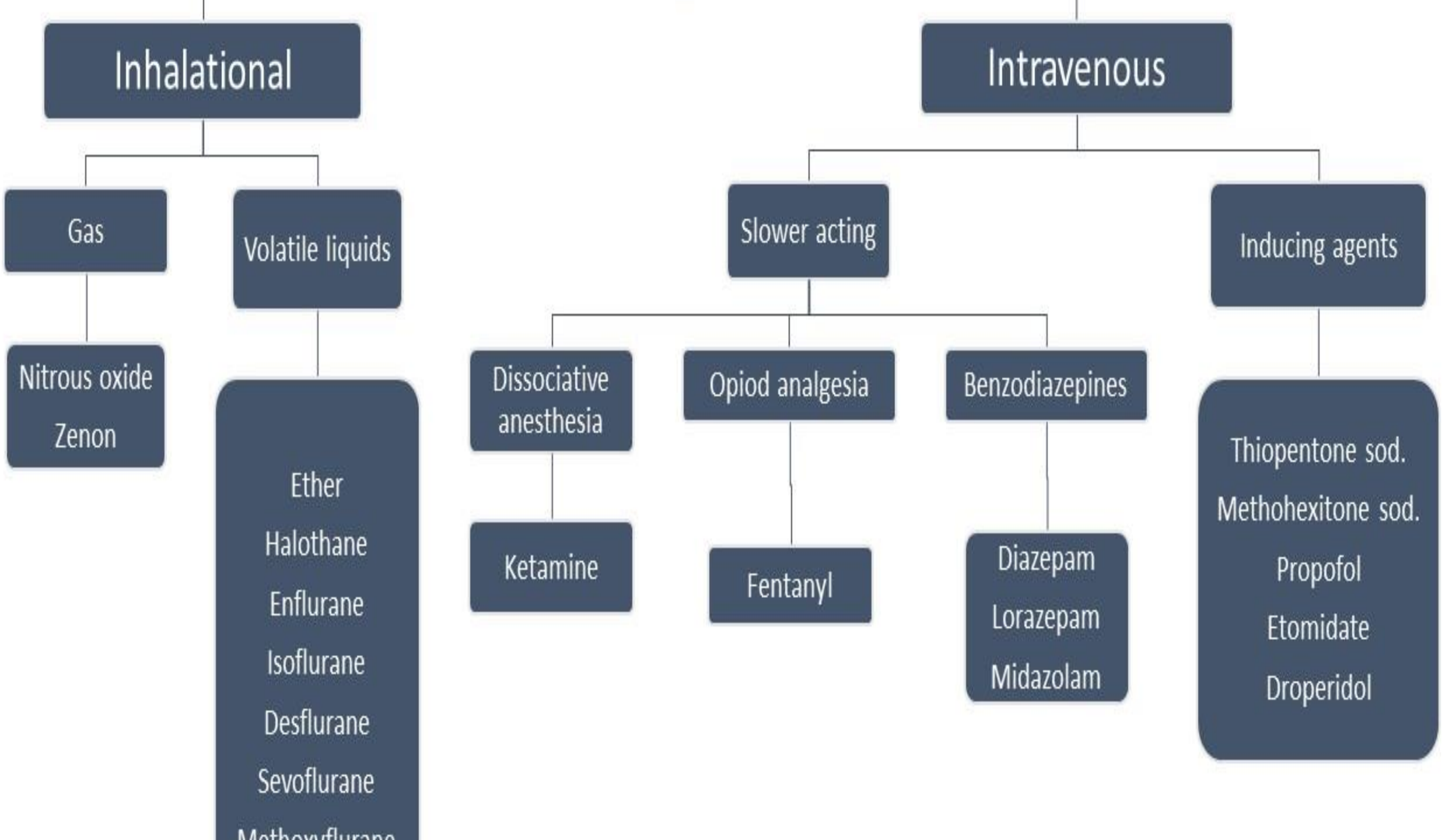

General Anesthesia
Inhalational
Intravenous
Gas
Volatile liquids
Slower acting
Inducing agents
Dissociative anesthesia
Opioid analgesia
Benzodiazepines
Nitrous oxide
Zenon
Ether
Halothane
Enflurane
Isoflurane
Desflurane
Sevoflurane
Methoxyflurane
Ketamine
Fentanyl
Diazepam
Lorazepam
Midazolam
Thiopental
Methohexital
Propofol
Etomidate
Droperidol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Diazepam
Lorazepam
Midazolam
Thiopentone sod.
Methohexitone sod.
Propofol
Etomidate
Droperidol

MECHANISM OF ACTION OF GENERAL ANAESTHETICS

Disruption of the function of ionic channels

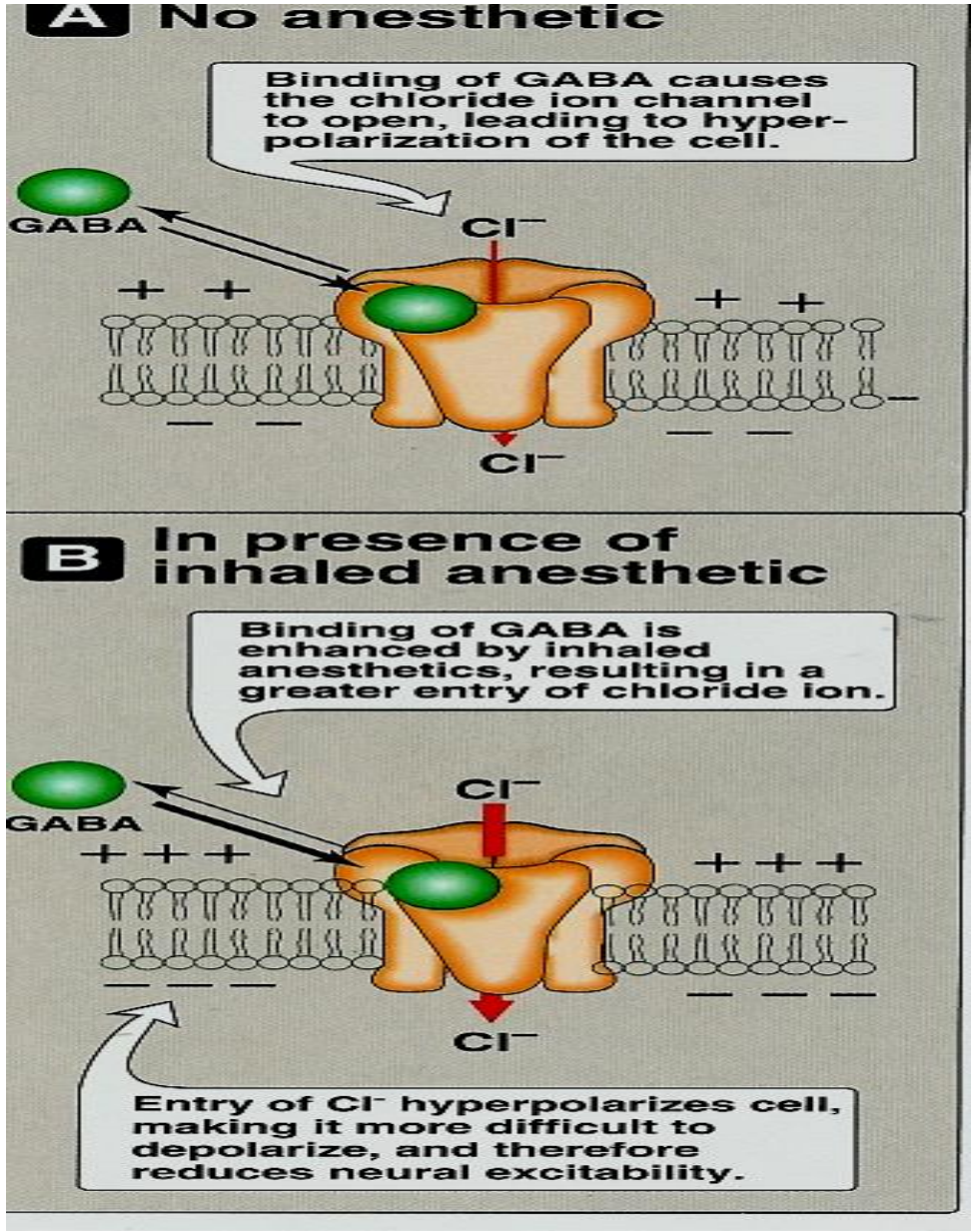
Disruption of lipids associated with ionic channels

Receptors

- **Inhibitory : GABA A, glycine**
- **Excitatory : nAch, NMDA**

MECHANISM OF ACTION OF GENERAL ANAESTHETICS

Enhance the action of $GABA_A$ and glycine on receptors leading to greater entrance of chloride ion → hyperpolarization → thus decrease neuronal excitability.



Inhalation anesthetics

Are halogenated hydrocarbons
End with suffix “flurane”

- **Methoxyflurane**
- **Halothane**
- **Enflurane**
- **Isoflurane**
- **Desflurane**
- **Sevoflurane**
- **Nitrous oxide**

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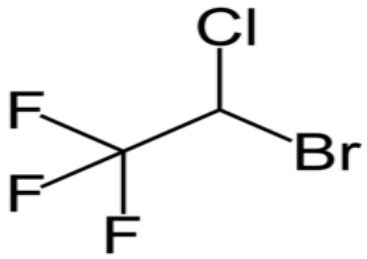
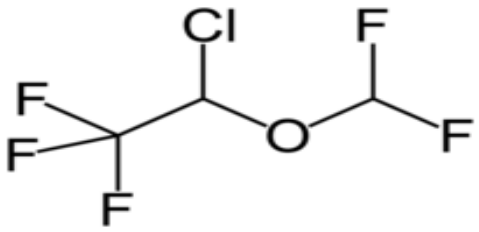
Structures

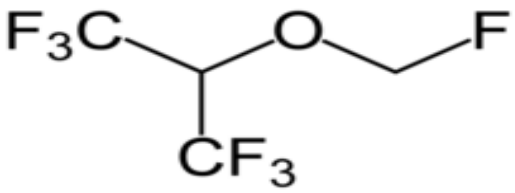
- **Inhalational**



Halothane



Isoflurane



Sevoflurane

Pharmacokinetics of Inhalation anesthetics

- **Rate of induction**
- **Depth of anesthesia and recovery.**

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Inhalation anesthetics

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.

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Pharmacokinetics of Inhalation anesthetics

Factors controlling induction & recovery

- **The anesthetic concentration in the inspired air: (Direct).**
- **Blood solubility:** Blood: gas partition coefficient **(Inverse relation).**
- **Rate and depth of ventilation (Direct).**

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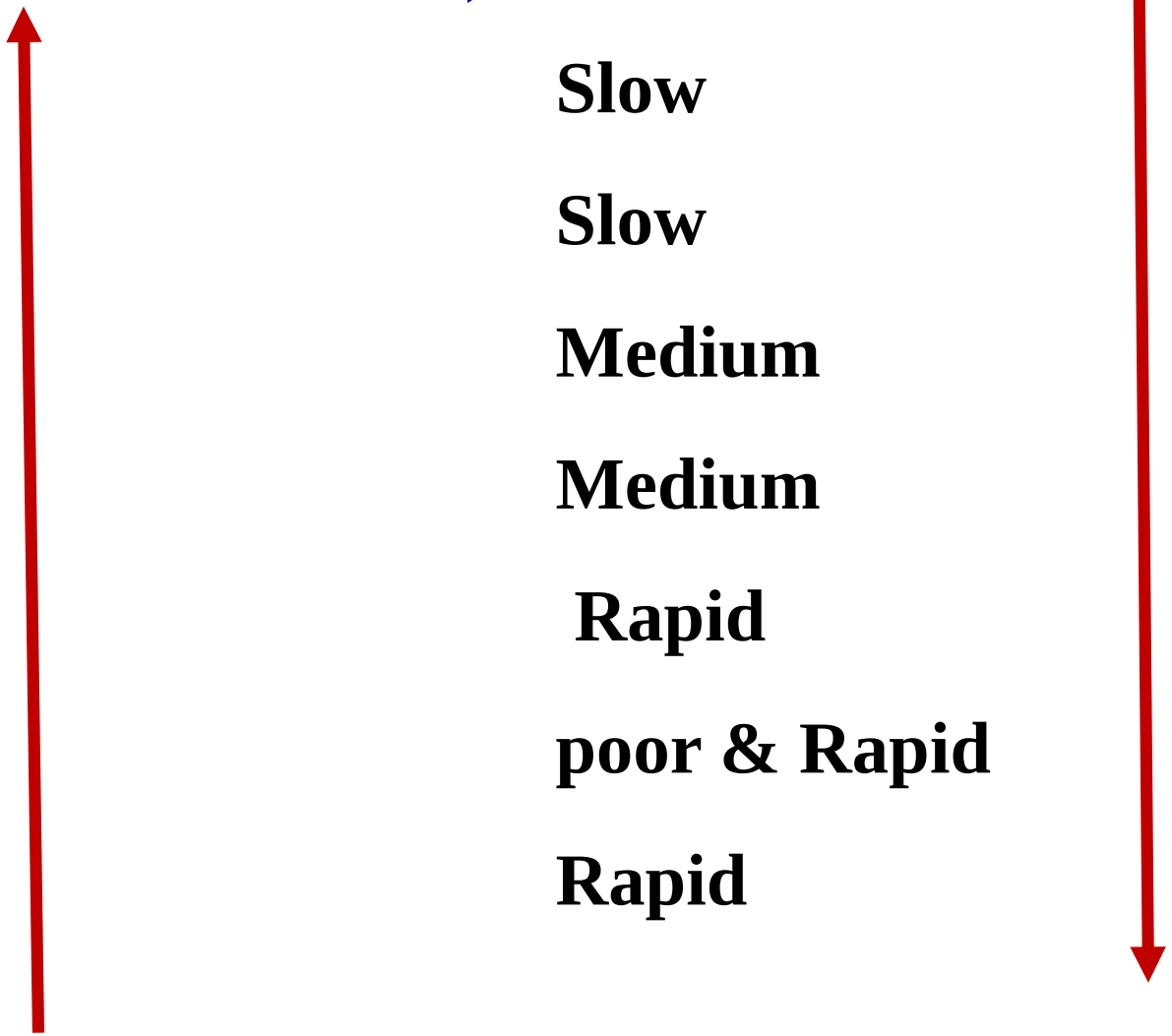
Drugs	Solubility (Blood : gas partition coefficient)	Induction & Recovery
Methoxyflurane	12	Slow
Halothane	2.3	Slow
Enflurane	1.8	Medium
Isoflurane	1.4	Medium
Sevoflurane	0.69	Rapid
Desflurane	0.42	poor & Rapid
Nitrous Oxide	0.47	Rapid



Minimum alveolar concentration (MAC)

- **It is the concentration of inhalation anesthetic that produce immobility in 50 % patients in response to surgical incision.**
- **Potency of anesthetic agents.**
- **Oil: gas partition coefficient (Direct with potency).**
- **The lower the MAC value the more potent the drug.**
- **Decreased by CNS depressants, old people.**
- **Increased by CNS stimulants.**

Drugs	MAC
Methoxyflurane	0.16
Halothane	0.75
Isoflurane	1.4
Enflurane	1.7
Sevoflurane	2
Desflurane	6-7
Nitrous oxide	>100

POTENCY

POTENCY & INDUCTION & VELOCITY

Drugs

Methoxyflurane: The most potent, low MAC value, **slow** induction& recovery

Halothane: Potent, **slow** induction & recovery (pleasant odor)

Enflurane: less potent, **medium** induction & recovery (pungent odor)

Isoflurane: less potent, **medium** induction & recovery

Sevoflurane : less potent, **rapid** induction & recovery (better smell)

Desflurane: **Rapid** induction & **rapid** recovery (pungent odor)

Nitrous oxide: The least potent, high MAC value, rapid induction & recovery

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Pharmacological actions of inhalation anesthetics

CNS

- ↓ metabolic rate.
- ↑ ICP (due to cerebral vasodilatation) # in head injuries.
- Dose -dependent EEG changes (Enflurane).

CVS

- Hypotension
- Bradycardia Except (Isoflurane & Desflurane).
- Myocardial depression (Halothane – Enflurane).
- Sensitize heart to catecholamines (Halothane)

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Pharmacological actions of inhalation anesthetics

Respiratory

- All respiratory depressants
-Airway irritation (Desflurane-Enflurane)

Liver

- Decrease hepatic flow
- Hepatotoxicity (Only halothane)

Uterus & Skeletal Muscles

-Uterine relaxation
- Nitrous oxide has minimal relaxant effect (labor).
- All are skeletal muscle relaxants.

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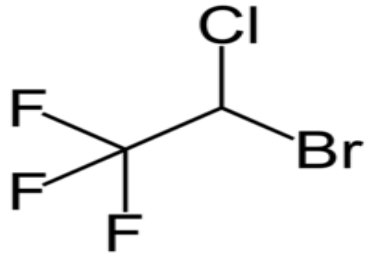
Halothane



- **Potent anesthetic, slow induction and recovery**
- **Weak analgesic, weak skeletal muscle relaxant.**
- **Metabolized to toxic metabolites (trifluroethanol) hepatotoxic.**
- **CVS depression**
    - **Hypotension, bradycardia (vagomimetic action)**
    - **↓ Myocardial contractility, ↓ Cardiac output**

Adverse Effects

1. **Hepatotoxicity (repeated use).**
2. **Malignant hyperthermia.**
3. **Cardiac arrhythmias.**
4. **Sensitizes heart to action of catechalamines → arrhythmias.**

Enflurane

- Less potent than halothane.
- Better muscle relaxation, Better analgesic properties.
- is metabolized to fluoride (8%), excreted in the kidney
- More rapid induction and recovery than halothane.

Disadvantages

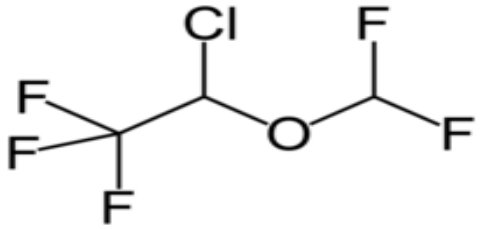
- Pungent (Less induction -Not for pediatrics).
- CNS stimulation (Epilepsy-like seizure- abnormal EEG).

Contraindication

- patients with seizure disorders.
- Not for renal failures.

Isoflurane (Forane)

- **Potent anesthetic, rapid induction & recovery**
- **Stable compound (2%).**
- **Low biotransformation (Less fluoride).**
- **No nephrotoxicity - No hepatotoxicity.**
- **Good analgesic action.**
- **No sensitization of the heart.**
- **No cardiac arrythmias.**



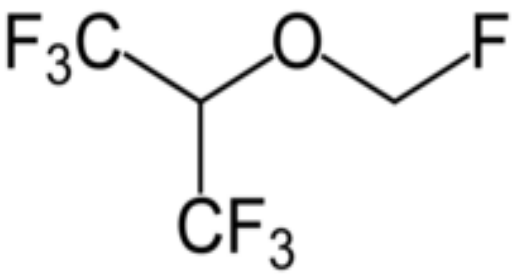
Disadvantages

Pungent (Not for pediatrics).

Desflurane

- **Pungent odor (irritation - Cough)**
- **Rapid induction & fast recovery (Low solubility).**
- **Less potent than halothane.**
- **Less metabolized (0.05 %).**
- **Low boiling point (special equipment).**

Sevoflurane



- **Better smell**
- **Less potent than halothane**
- **Rapid onset and recovery (Low solubility)**
- **Less metabolized (3- 5% fluoride)**
- **Little effect on HR**
- **No airway irritation (preferable for children)**

Nitrous Oxide (N2O)

- **Potent analgesic.**
- **Weak anesthetic (Low potency, combined).**
- **Rapid induction & Recovery (Low solubility).**
- **No muscle relaxation, No respiratory depression.**
- **Not hepatotoxic, minimal CVS adverse effects.**

Adverse Effects

1. **Diffusion Hypoxia: (respiratory diseases).**
2. **Nausea and vomiting.**
3. **Inactivation of B 12 $\longrightarrow$ megaloblastic anemia.**
4. **Bone marrow depression-Leukopenia (chronic use).**
5. **Abortion - Congenital anomalies**

Therapeutic Uses

1. **Outpatient anesthesia (Dental procedures).**
2. **Balanced anesthesia.**
3. **Neuroleptanalgesia.**
4. **Delivery**

Contraindications

1. **Pregnancy.**
2. **Pernicious anemia.**
3. **Immunosuppression.**

Inhalation anesthetics

Anesthetic drugs	Characters
Methoxyflurane	For veterinary use only
Halothane	Non irritant - Potent anesthetic, Weak analgesic. Can be used in children
Isoflurane	Stable compound (2%), Low biotransformation (Less fluoride). No nephrotoxicity - No hepatotoxicity.
Enflurane	is metabolized to fluoride (8%) Contraindicated in patients with seizure disorders. Not for renal failures.
Desflurane	Less metabolized (0.05 %), low boiling point (special equipment)
Sevoflurane	Better smell, little effect on HR, No airway irritation (children)
Nitrous oxide	Potent analgesics, Minimal CVS adverse effects, contraindicated in pregnancy

Side effects of inhalation anesthetics

Anesthetic drugs	Side effects
Methoxyflurane	Slow induction, nephrotoxicity
Halothane	Slow induction and recovery (??????). Sensitization of heart to catecholamines Hepatotoxicity, Malignant hyperthermia
Desflurane	Pungent odor, Airway irritation
Enflurane	Pungent (less induction -Not for pediatrics). Airway irritation CNS stimulation (Epilepsy-like seizure- abnormal EEG).
Nitrous oxide	Weak anesthetic (low potency, combined). Diffusion hypoxia, Nausea and vomiting. Inactivation of B 12 ⟶ megaloblastic anemia, congenital anomalies

General Anesthesia

Intravenous

Slower acting

- Dissociative anesthesia
  - Ketamine
- Opioid analgesia
  - Fentanyl
- Benzodiazepines
  - Diazepam
  - Lorazepam
  - Midazolam

Inducing agents

- Thiopental
- Methohexital
- Propofol
- Etomidate
- Droperidol

Intravenous anesthetics

- Ultra short acting barbiturates e.g. thiopental, methohexital
- Benzodiazepines (diazepam, lorazepam, midazolam)
- Opioids (fentanyl)
- Ketamine
- Propofol
- Etomidate

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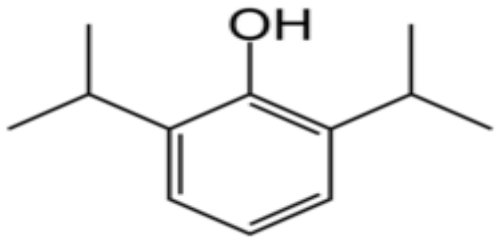
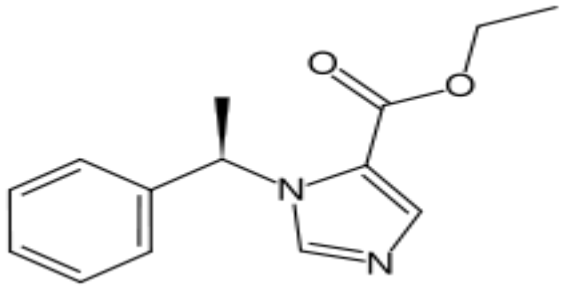
Structures

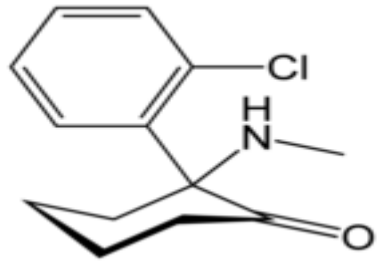
- Intravenous



Propofol

Etomidate





Ketamine

Intravenous anesthetics

- **NO need for special equipments.**
- **Rapid induction & recovery EXCEPT benzodiazepines**
- **Injected slowly (rapid induction).**
- **Recovery is due to redistribution from CNS.**
- **Analgesic activity: Opioids & ketamine**
- **Amnesic action: benzodiazepines & ketamine.**
- **Can be used alone in short operation & Outpatients anesthesia.**

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CHARACTER S OF INTRAVENOUS ANAESTHETIC DRUGS

Drug	Induction and recovery
Thiopental	Fast onset, slow recovery, hangover
Etomidate	Fast onset, fairly fast recovery, less hangover
Propofol	Fast onset, rapidly metabolized, very fast recovery
Ketamine	Slow onset, **Dissociative anesthesia** Produces good analgesia and amnesia.
Fentanyl	Slow onset
Midazolam	Slower onset than other agents, has amnesic effect

Ultrashort acting barbiturates

e.g. Thiopental, Methohexital

- **Rapid onset of action 1 min (high lipid solubility).**
- **Ultra short duration of action 15 - 20 min**
- **Metabolized slowly by the liver (slow recovery)**
- **Potent anesthetic.**
- **CNS: ↓ ICP (Used in head injuries).**
- **CVS collapse & respiratory depression, precipitate porphyria attack, hypersensitivity reaction.**
- **Used for induction in major surgery and alone in minor surgery.**

Propofol

- **Hypnotic (Non Barbiturate).**
- **Rapid onset, short duration of action, Faster recovery than thiopental**
- **Rapidly metabolized in liver (10 times - Elimination ½ = 30 – 60 min).**
- **Decreases ↓ ICP**
- **Has Antiemetic action.**

Side Effects

- **Hypotension (↓PVR).**
- **Excitation (involuntary movements), Pain at site of injection**
- **Expensive, Clinical infections due to bacterial contamination**

Benzodiazepines

e.g. Midazolam, Diazepam , Lorazepam

- **No pain, have anxiolytic and amnesic action**
- **Slow induction & recovery.**
- **Cause respiratory depression.**
- **Used in induction of general anesthesia.**
- **Alone in minor procedure (endoscopy).**
- **In balanced anesthesia (Midazolam).**

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Etomidate

- Ultrashort acting hypnotic (Non Barbiturates).
- Rapid onset of action, short duration of action.
- Rapidly metabolized in liver (less hangover).
- Minimal CVS and respiratory depressant effects.
- Involuntary movements during induction (diazepam).
- Postoperative nausea & vomiting.
- Pain at sit of injection.
- Adrenal suppression

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ketamine

- **Dissociative anesthesia (Analgesic activity, amnesic action, immobility, complete separation from the surrounding environment).**
- **Rapid onset of action, short duration, is given IV, IM (Children).**
- **↑ BP & cardiac output (↑central sympathetic activity).**
- **↑ Increases plasma catecholamine levels, ↑ ICP**
- **Potent bronchodilator (asthmatics).**
- **Used in (hypovolemic, shock & elderly) patients.**
- **Post operative hallucination vivid dreams & disorientation &illusions**
- **Risk of hypertension & cerebral hemorrhage, ↑ ICP**

Opiate drugs

Fentanyl, Alfentanil, Sufentanil, Remifentanil

Rapid onset, Short duration of action, Potent analgesia.

Uses

Neuroleptanalgesia (Fentanyl + Droperidol).
Neuroleptanesthesia (Fentanyl+Droperidol+ nitrous oxide).

Side Effects

Respiratory depression, bronchospasm (wooden rigidity).
Hypotension, nausea & vomiting

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Contraindication

1. **Head injuries.**
2. **Pregnancy.**
3. **Bronchial asthma.**
4. **Chronic obstructive lung diseases.**
5. **Hypovolemic shock (Large dose only).**

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Neuroleptanalgesia

- A state of analgesia, sedation and muscle relaxation without loss of consciousness.
- used for diagnostic procedures that require cooperation of the patient.
- Innovar (Fentanyl + Droperidol).
- Contraindicated in parkinsonism.

Neuroleptanesthesia

A combination of (Fentanyl + Droperidol + nitrous oxide).

EFFECTS OF INTRAVENOUS DRUGS ON CVS SYSTEM

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

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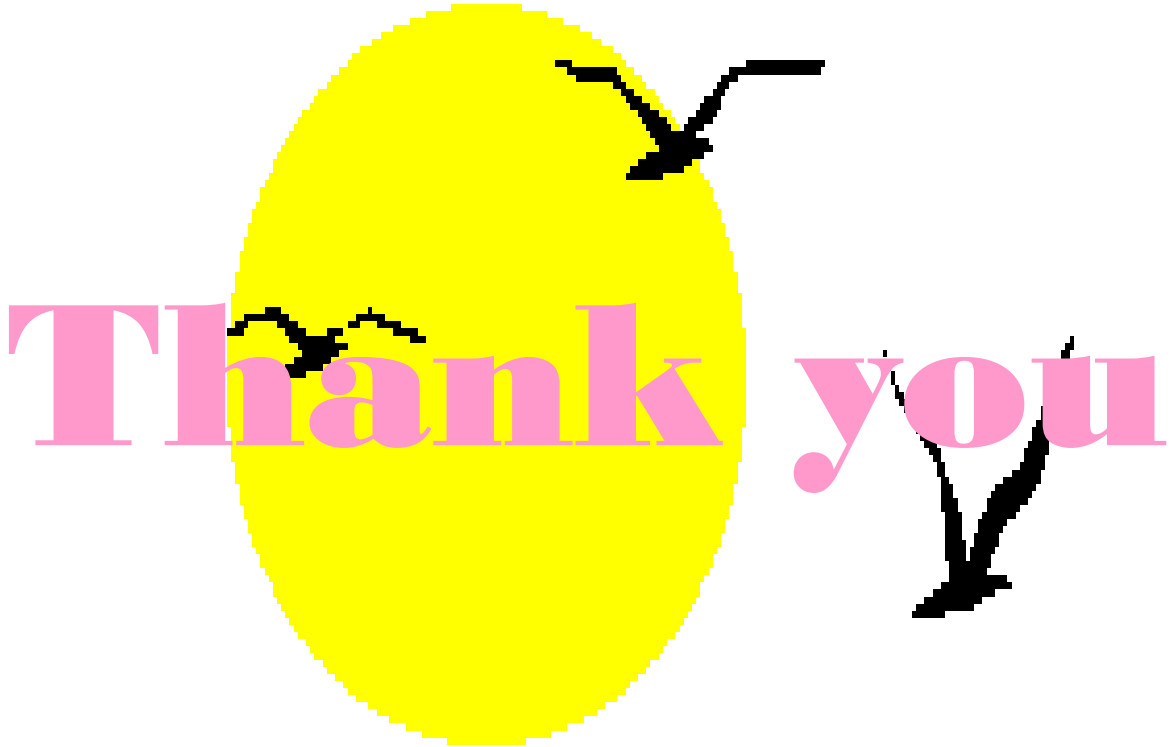
SIDE EFFECTS OF INTRAVENOUS ANAESTHETIC DRUG

Drug	Main side effects
Thiopental	CVS collapse and respiratory depression (Laryngospasm, bronchospasm), porphyria
Etomidate	**Adrenocortical suppression, Excitatory effects during induction** pain at site of injection, Post-operative NV
Propofol	CVS and respiratory depression, Excitation (involuntary movements) Pain at injection site, expensive.
Ketamine	Psychotomimetic effects following recovery **(vivid dreams, hallucination**) Postoperative nausea, vomiting，salivation Risk of hypertension and cerebral hemorrhage
Midazolam	Slow induction & recovery Minimal CVS and respiratory depression
Opioids **Fentanyl**	Respiratory depression, Bronchospasm (wooden rigidity). Hypotension, Nausea & vomiting, Increase in ICP, Urinary retention. Prolongation of labor & fetal distress.

CONTRAINDICATION OF INTRAVENOUS ANAESTHETIC DRUGS

Drug	Contraindications
Thiopental	Porphyria, severe hypotension (**hypovolemic & shock patient**) **Chronic obstructive lung disease.**
Propofol	CVS and respiratory depression
Fentanyl	Head injuries, Pregnancy, Bronchial asthma, Chronic obstructive lung diseases. Hypovolemic shock (Large dose only).
Ketamine	CV diseases (hypertension-stroke). Head injuries.
Midazolam	Respiratory patients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