

6. GENERAL ANESTHESIA

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DEFINITION:

“General anesthetics are drugs that act in the central nervous system. They produce reversible loss of consciousness, thereby causing a generalized loss of sensation.”

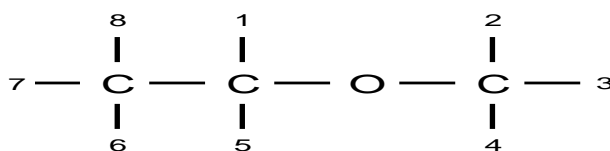
HISTORY OF GENERAL ANESTHESIA:

- Joseph Priestly – discovers N₂O in 1773
- Sir Humphrey Davy – experimented with N₂O, reported loss of pain, euphoria
- 1842, Crawford Long – First used ether. Did not publicize. Tried to claim credit after Morton’s demonstration but...
- Important lesson learned – if you don’t publish it, it didn’t happen.
- 1846, William Morton, dentist – Diethyl Ether – First demonstration of successful surgical anesthesia - administered ether to a patient having a neck tumor removed at the Massachusetts General Hospital, Boston, in October 1846.
- 1847, James Simpson – Chloroform
- 1930s, Intravenous Barbiturates
- 1940s, d-Tubocurarine to induce skeletal muscle relaxation
- 1956, Halothane (halogenated hydrocarbon)
- 1981, Isoflurane (currently most popular)

PHYSICAL AND CHEMICAL PROPERTIES OF INHALED ANESTHETICS

- Although halogenations of hydrocarbons and ethers increase anesthetic potency, it also increase the potential for inducing cardiac arrhythmias in the following order $F < Cl < Br$.
- Ethers that have an asymmetric halogenated carbon tend to be good anesthetics (such as Enflurane).
- Halogenated methyl ethyl ethers (Enflurane and Isoflurane) are more stable, are more potent, and have better clinical profile than halogenated diethyl ethers.
- Fluorination decrease flammibility and increase stability of adjacent halogenated carbons.
- Complete halogenations of alkane and ethers or full halogenations of end methyl groups decrease potency and enhances convulsant activity. Flurorhyl (CF₃CH₂OCH₂CF₃) is a potent convulsant, with a median effective dose (ED₅₀) for convulsions in mice of 0.00122 atm.
- The presence of double bonds tends to increase chemical reactivity and toxicity.

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	MW	1	2	3	4	5	6	7	8
Diethyl ether	74	H	H	CH ₃	H	H	H	H	H
Fluroxene	126	H	H	=CH ₂		H	F	F	F
Methoxyflurane	165	F	H	H	H	F	Cl	H	Cl
Desflurane	168	H	F	H	F	F	F	F	F
Isoflurane	184	H	F	H	F	Cl	F	F	F
Enflurane	184	F	F	H	F	F	Cl	H	F
Sevoflurane	200	H	H	F	H	CF ₃	F	F	F

CHARACTERISTICS OF IDEAL ANESTHETICS:

- It has the high lipid solubility because the higher the solubility of anesthetics is in oil, the greater is the anesthetic potency.
- Its action must be irreversible.
- It should be non irritant to tissue.
- It should be good muscles relaxant.
- It should have the low degree of systemic toxicity.
- It should be stable in light.
- It should not produce any permanent damage.
- It should have non inflammable properties.
- It should be non addictive.

GENERAL ANESTHETIC PROTOCOLS

- No single agent alone meets all criteria
- Combinations to maximize favorable effects and minimize untoward effects
- Anesthetics have low therapeutic index.
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- Combinations to maximize favorable effects and minimize untoward effects
- Anesthetics have low therapeutic index

Minor Procedures: Oral sedatives and regional local anesthesia.

Conscious Sedation: IV benzodiazepines and opioid analgesics (can respond to verbal commands, patent airway)

Major Surgical Procedures: Preoperative sedatives (anxiolytic, amnesia), muscle relaxants, atropine (to limit mucous secretions)

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Induction of anesthesia: IV thiopental, propofol, etomidate or benzodiazepine (esp. midazolam).

Deep anesthesia: Inhaled anesthetics and IV anesthetics

ROUTES OF INDUCTION:

1. **Intravenous:** Safe, pleasant and rapid
2. **Mask:**
 - Common for children under 10
 - Most inhalational agents are pungent, evoke coughing and gagging
 - Avoids the need to start an intravenous catheter before induction of anesthesia
 - Patients may receive oral sedation for separation from parents/caregivers
3. **Intramuscular:** Used in uncooperative patients

CLASSIFICATIONS OF GENERAL ANESTHETICS AGENTS:

1. Inhalation:

a. **Gas:** Nitrous Oxide

b. **Volatile Liquids:**

Ether

Halogenated hydrocarbon: Chloroform (CHCl_3), Halothane (Br-, Cl- and F-substituted) – High lipid soluble

Halogenated ethers: Enflurane, Isoflurane (Cl- and F-substituted (more lipid sol.))

Desflurane, Sevoflurane (Only F-substituted (less lipid soluble))

2. Intravenous:

a. **Barbiturates:** Thiopental

b. **Benzodiazepines:** Midazolam, diazepam

c. **Opioid Agonists:** Morphine, fentanyl, sufentanil, remifentanyl

3. **Dissociative Anesthesia:** Ketamine

4. **Neurolept anesthesia:** Droperidol

5. **Others:**

Propofol, etomidate

1. INHALATION GENERAL ANESTHETICS:

Mechanism of action:

- Activate inhibitory receptors (ligand-gated Cl⁻ channels):
 - GABA-A-receptor: Inhalation anesthetics, except nitrous oxide.

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- GLYCINE-receptor: Inhalation anesthetics, except nitrous oxide
- General anesthetics INHIBIT excitatory receptors (ligand-gated Na⁺ channels):
 - Ach-receptor (neuronal N-type): All inhalation anesthetics
 - Glu-receptor (NMDA type): Nitrous oxide
- It has primary effects on synaptic processes to decrease neuronal activity.
- Volatile anesthetics may block the central ($\alpha 7$) nicotinic cholinergic receptor and the 5-HT₃ receptor.
- Volatile agents may activate and open the 2 pore K⁺ channels to cause hyperpolarization.

a. Anesthetic gases:

i. Cyclopropane:

- It is an obsolete agent.
- Currently it is not used because of it is flammable and explosive.
- It sensitizes the heart to catecholamines, and can induce arrhythmias, including ventricular fibrillation.

ii. Nitrous oxide (N₂O):

- It is known as laughing gas.
- It produces euphoria.
- It is the least lipid soluble and least potent inhalation anesthetic (MAC = 105%). As a single anesthetic agent, it could be used reliably only under hyperbaric conditions.

Advantages:

- ✓ N₂O is nonflammable, not explosive.
- ✓ It lacks harmful effects under proper use.
- ✓ It does not induce malignant hyperthermia.
- ✓ Of the inhalation anesthetics, N₂O is least likely to increase cerebral blood flow and intracranial pressure.
- ✓ It promotes induction and recovery when combined with halothane.

Disadvantages:

- ✓ N₂O is very weak so it used only in combination with other general anesthetics.
- ✓ It has no muscle relaxant activity so required muscle relaxant agent.
- ✓ It produces hypoxia.

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b. Volatile liquid:

i. Ethers: No longer used

Diethyl ether

- Ether produces good muscle relaxation.
- Ether is a safe anesthetic.
- It does not have severe toxic effects (e.g., hepato- and nephrotoxicity), and it does not depress cardiac contractility and respiration markedly (mechanical ventilation is not required). In contrast, all halogenated inhalation anesthetics (as well as barbiturates and propofol) have respiratory depressive effect, necessitating mechanical ventilation.
- It is also rarely used due to its flammability.

Divinyl ether: $\text{CH}_3\text{-CH}_2\text{-O-CH}_2\text{-CH}_3$

- Divinyl ether is not used nowadays mainly because of the flammability and explosiveness of its vapor.
- Divinyl ether is more potent than diethyl ether, and is less irritative to the airways.
- May be used for short anesthesia to reach the stage of analgesia for a short surgical intervention, e.g., for removal of pharyngeal tonsils.

ii. Chloroform (CHCl_3):

It is introduced in 1847 by James Simpson, a Scottish obstetrician. Queen Victoria delivered her 8th child in chloroform anesthesia (after which JS was knighted).

Its sweetish odor made chloroform popular, but it is no longer used because of its hepato- and cardiotoxicity.

iii. Halothane (Narcotan):

- It is the only inhalational anaesthetic agent containing a bromine atom.
- Its use is limited due to its idiosyncratic hepatotoxicity.

Advantages:

- ✓ It is non-flammable.
- ✓ It not produces delirium as well as cause smooth induction.
- ✓ It rarely induces postoperative nausea and vomiting.
- ✓ It has bronchodilatory effect.

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Disadvantages:

- ✓ Insufficient decrease of muscle tone (easily overcome by muscle relaxants).

iv. Enflurane (Ethrane):

- Its use is limited.
- Mostly it is use in combination.
- It have dual properties means some of the properties of diethyl ether and some of the properties of halothane.

Advantages:

- ✓ It has a good muscle relaxant effect.
- ✓ It does not sensibelize the heart toward catecholamines.
- ✓ It is not flammable.
- ✓ It smoothly induces anesthesia.

Disadvantages:

- ✓ It is mildly stimulates the tracheobronchial secretions.
- ✓ It may cause postoperative nausea and vomiting (10%).
- ✓ It decreases cardiac contractility but not produce effect on the heart rate so it causes a moderate decrease in cardiac output and blood pressure.
- ✓ It depresses the respiration and increase $p\text{CO}_2$ so ventilation is needed.

v. Isoflurane (Forane; an isomer of enflurane):

- ✓ The most commonly used volatile anesthetic today.

The main advantages over enflurane are:

- ✓ Isoflurane's dehalogenation in the body is only 0.2%, there is no reason to fear toxic metabolite(s).
- ✓ Isoflurane does not cause cardiac depression so cardiac output is well maintained. It decreases BP because it reduces peripheral vascular resistance (including the coronary) as well as it increases the heart rate, but arrhythmias are not precipitated.
- ✓ It does not induce seizures.
- ✓ It is a preferred anesthetic for BRAIN SURGERY for 2 reasons:
It decreases O_2 demand/utilization by the brain.

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Although isoflurane slightly increase the cerebral blood flow (CBF), the CBF and ICP can be decrease by inducing hypocarbia (low pCO₂) with hyperventilation. (Hypocarbia causes cerebral vasoconstriction.)

An unfavorable property:

- ✓ Isoflurane has pungent odor and irritates airways.
- ✓ This necessitates induction with an i.v. anesthetic.

vi. Methoxyflurane (Penthrane):

- ✓ It is mostl useful for inducing the stage of analgesia, but not for general anesthesia.
- ✓ Its use as a general anesthetics has been discontinued due mainly to its nephrotoxic effect.

vii. Desflurane (Suprane) and sevoflurane (Ultane):

- ✓ Often used inhalation anesthetics nowadays.
- ✓ They do not cause cardiac depression.

2. INTRAVENOUS GENERAL ANESTHETICS:

It is mainly hydrophobic and lipophilic compounds

Mechanism of actions:

- Activate inhibitory receptors (ligand-gated Cl⁻ channels):
 - GABA-A-receptor all I.v. anesthetics, except ketamine.
- General anesthetics INHIBIT excitatory receptors (ligand-gated Na⁺ channels)
 - Ach-receptor (neuronal N-type) e.g. Barbiturate-type i.v. anesthetics
 - Glu-receptor (NMDA type) e.g. Ketamine

i. Barbiturates: thiopental (a thiobarbiturate) and methohexital (an oxobarbiturate)

- Dose for methohexital: 1-1.5 mg/kg iv, for thiopental: 3-5 mg/kg i.v.
- Onset of action: ~20 sec; induction is rapid and smooth
- Duration of action: ~5-10 min, for both

Advantages of barbiturates:

- ✓ Barbiturates decrease the cerebral metabolic rate and O₂ utilization by the brain so decrease the cerebral blood flow and decrease intracranial pressure (an advantage in brain surgery) as well as decrease intraocular pressure
- ✓ Barbiturates exert anticonvulsive effect e.g.: thiopental is valuable in the treatment of status epilepticus

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Disadvantages:

- ✓ Incompatibility: The injectable solution is basic (pH 10-11) as barbiturates are dissolved as Na-salts; if mixed with acidic solutions (e.g., a muscle relaxant, such as pancuronium bromide) the barbiturate precipitates out as a free acid!
- ✓ Barbiturates exert vascular irritative effect: - if the i.v. injected thiopental conc. is $>2.5\%$, it may induce pain and thrombophlebitis - if injected intra-arterially, it induces endarteritis and gangrene! (The pain resulting from the veno-irritative effect can be prevented by prior injection of lidocaine.)
- ✓ Barbiturates induce respiratory depression (low minute volume) and apnea at high dose. In asthmatics, they may induce histamine release and wheezing.
- ✓ Barbiturates induce hypotension by causing both: - vasodilatation, and - negative inotropic effect. Therefore, barbiturates should not be injected - too rapidly and excessive decrease in cardiac contractility, and - to a patient who cannot compensate for decrease blood pressure, e.g. those with - hypovolemia - cardiomyopathy - coronary artery disease - β -receptor blockade
- ✓ Barbiturates induce ALA synthetase, the first enzyme in heme synthesis. This in turn will cause accumulation of porphyrins (neurotoxic byproducts of heme synthesis) in patients deficient in some downstream enzymes of the heme synthetic pathway. Thus barbiturates may precipitate widespread demyelination in patients with - Acute intermittent porphyria (deficiency in porphobilinogen deaminase), and - Variegate porphyria (deficiency in protoporphyrinogen oxidase). In these inherited porphyrias barbiturates are absolutely contraindicated.

ii. Propofol (DIPRIVAN - 2,6-diisopropylphenol):

- It is an often used anesthetic, especially for TIVA
- Dose: 1.5-2.5 mg/kg
- Onset and duration of anesthesia:
 - After a bolus dose, anesthesia develops in ~ 20 sec, like for barbiturates
 - recovery is $>$ within 10 min after a 3-hr infusion

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- and > within 40 min after an 8-hr infusion
- Used for:
 - Total Intravenous Anesthesia (TIVA) in infusion (0.1-0.2 mg/kg/min)
 - For example, TIVA is used by orthopedic surgeons in SCOLIOSIS CORRECTION SURGERY, which - requires anesthesia for several hours, however, - the patient has to be wakened up (by stopping propofol infusion) to test sensory and motor functions after reposition of the spinal column and before completing the surgery.
 - Also used for continuous sedation in intensive care units (ICU) – be aware of the possibility of (Propofol Infusion Syndromes) PRIS

Advantages:

- Propofol decrease cerebral metabolic rate so decrease O₂ consumption.
- As well as decrease cerebral blood flow, intracranial and intraocular pressure.
- Propofol has antiemetic effect.

Disadvantages:

- Propofol has veno-irritative effect produce pain which is prevented by lidocaine i.v. administration.
- It has respiratory depressive effect (stronger than barbiturates) and decreases blood pressure because of vasodilatation and negative inotropic effect.
- Propofol is a water immiscible oily substance. Its emulsion is used as an i.v. anesthetic. Its solvent contains soybean oil, egg phospholipids and glycerol, which supports bacterial growth. To overcome this problem, the water soluble prodrug of propofol, fospropofol is now marketed as Lusedra in the USA. Fospropofol is the phosphate ester of propofol, which is hydrolyzed by alkaline phosphatase (AP) in the body, thus releasing propofol.
- Propofol produce PRIS reaction: PRIS is caused by toxic effect of propofol on mitochondria, mainly in skeletal and cardiac muscle. Propofol acts as a weak protonophoric uncoupler: it diffuses into mitochondria, dissociates its phenolic proton, thus dissipating the inwardly directed H⁺ gradient that drives ATP synthase. In addition, propofol also inhibits mitochondrial electron transport.

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- Consequences and signs of the mitochondrial toxicity of propofol:
Cardiac failure: acute refractory bradycardia (may lead to asystole), hypotension, and ST elevation.

Rhabdomyolysis: Increase serum K^+ , Increase serum creatine kinase (CK), myoglobinuria which leads to renal failure

Hepatomegaly with fatty liver (probably caused by inhibition of fatty acid oxidation)

High serum triglyceride levels (may be an early marker; caused by inhibition of fatty acid oxidation?)

Lactic acidosis (pyruvate use by PDH complex is impaired and pyruvate is reduced to lactate by LDH)

iii. Etomidate (AMIDATE):

- Dose: 0.2-0.4 mg/kg
- Rapidly and ultra short acting (4-8 min) anesthetic which is used mainly for induction of anesthesia
- Its prolonged infusion is contraindicated because it inhibits cortisol synthesis and blunts the stress response (may increase mortality).

Advantages:

- It decrease cerebral metabolic rate and O_2 consumption so decrease the cerebral blood flow, intracranial and intraocular pressure
- It causes little respiratory depression and little or no decrease in blood pressure and may slightly increase the heart rate
- The cardiovascular function is stable during etomidate anesthesia.
- Etomidate is usually reserved for patients at risk for hypotension and/or myocardial ischemia

Disadvantages:

- It often induces nausea and vomiting
- It causes pain on injection (like barbiturates and propofol; prevent it by prior injection of lidocaine)
- Appears to have proconvulsive effect (contraindicated in seizures/epilepsy).

iv. Ketamine:

- Ketamine has analgesic effect that outlasts the anesthetic effect it is an advantage.

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- Ketamine may be used by ambulance services for sedation and pain suppression in patients.
- Ketamine may induce disagreeable dreams and hallucinations, when emerging from the anesthesia. This occurs seldom in children.
- Ketamine is a preferred anesthetic in pediatric surgery (may be given in combination with a benzodiazepine).
- Ketamine has indirect sympathomimetic effect because it decrease neuronal reuptake of catecholamines both peripherally and centrally (like cocaine) this effects produces increase in blood pressure, increase in heart rate, cardiac output and myocardial O₂ consumption. It increase cerebral blood flow and intracranial pressure as well as produce papillary dilation, nystagmus, lacrimation and bronchodilation.
- ketamine is indicated for patients who are at risk for hypotension (like etomidate), who are asthmatic.
- It is contraindicated for patients who are at risk for myocardial ischemia and who have increase intracranial pressure.

v. Opioids:

- It is high potent drugs, i.e., fentanyl or one of its congeners i.v.
- Fentanyl is a relatively long acting opioid (T_{1/2} = 4 hrs): 100-150 µg/kg
- Sufentanyl – a super potent opioid: 0.25-0.5 µg/kg, (T_{1/2} = 2 hrs)
- Remifentanyl, It is an ultrashort acting opioid (a diester that is rapid hydrolyzed by carboxylesterases) T_{1/2} = 4 min; infused i.v. at a rate of 0.1-0.5 µg/kg/min.
- Remifentanyl may be used for TIVA with propofol (the dose rate for propofol then should be reduced).
- Unwanted effects of opioids: - Respiratory depression, Chest wall and laryngeal rigidity, Decreased gastrointestinal and bladder motility. These effects are dose-dependent and are easily controlled with the use of the ultrashort acting remifentanyl by adjusting its infusion rate.
- Combination of opioids with benzodiazepines – causes general anesthesia.
- Combination of opioids with butyrophenones – causes neurolept analgesia as well as antipsychotic effects.