General Anesthetic Drugs.

Before Anesthetics

- Surgery uncommon
- Surgical pain relief
  - alcohol, opium
  - physical methods (ice, ischemia)
  - unconsciousness (blow to head, strangulation)
- simple restraint most common
General anesthetics primary effects:
Unconsciousness.
Amnesia.
Analgesia.
inhibition of autonomic reflexes.
skeletal muscle relaxation.

None of the available anesthetic agents can achieve all five of these desired effects.

An ideal anesthetic drug should:
  induce rapid smooth loss of consciousness.
  rapidly reversible upon discontinuation,
  possess a wide margin of safety.

The modern practice use combinations of IV and inhaled drugs (balanced anesthesia techniques)
Mechanism of General Anesthetic Action

Anesthetics enhance inhibitory postsynaptic channel activity (\textbf{GABA A and glycine} receptors)
Anesthetics inhibit excitatory synaptic channel activity (nicotinic \textbf{acetylcholine} and \textbf{glutamate} receptors)
Inhaled Anesthetics

Uptake & Distribution

*Inspired Concentration and Ventilation*

The uptake depends on the alveolar concentration which depends on:

(1) *inspired concentration* or *partial pressure.*

The increase of partial pressure in the alveoli is expressed as a ratio of alveolar concentration (FA) over inspired concentration (FI).

- the faster FA/FI approaches 1 the faster anesthesia will occur during an inhaled induction.

Inspired concentration (*higher concentration, faster*)
(2) *alveolar ventilation.*

Ventilation rate (increased rate, faster)

Hyperventilation increases the speed of induction of anesthesia.

Alveolar tension of anesthetic gas of low solubility after 10 breathing cycles.

Alveolar tension approaches inspired tension.
Factors Controlling Uptake

The increase of FA/FI is opposed by the uptake of anesthetic into the blood.

Solubility

The blood:gas partition coefficient is the relative affinity of an anesthetic for the blood compared with that of inspired gas. (less soluble, faster)
# General Anesthetics: Solubility

<table>
<thead>
<tr>
<th>Partition Coefficient</th>
<th>Blood:Gas</th>
<th>Brain:Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Poorly soluble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>0.46</td>
<td>1.1</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>1.3</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.59</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Cardiac output decreased COP, faster.

The alveolar to venous partial pressure difference large difference, slower.
Elimination

Rate of recovery depends on: blood solubility, COP, ventilation & tissue solubility.

Recovery of nitrous oxide, desflurane & sevoflurane (Low blood solubilities) at rapid rate, compared with halothane and isoflurane.

Ventilation

Ventilation is the only way to speed recovery.

Metabolism

Metabolism is important for their toxicity.
STAGES OF GENERAL ANESTHESIA (Guedel)

I: Analgesia Stage analgesia without amnesia. Later in stage I, both analgesia and amnesia are produced.

II: Excitement/ Delirium Stage delirious, may vocalize, respiration is rapid, HR & BP increase.

III: Surgical Anesthesia begins with slowing of respiration and heart rate and extends to complete cessation of spontaneous respiration (apnea).

Four planes of stage III are described
- Plane I: reg. breathing, loss of eye movement
- Plane II: initiation of IC muscle paralysis
- Plane III: completion ICM paralysis
- Plane IV: diaphragmatic paralysis

Stage IV: Medullary Paralysis

MAC = Minimum Alveolar Concentration
Alveolar tension required to produce surgical anesthesia in 50% of patients

<table>
<thead>
<tr>
<th>ANESTHETIC</th>
<th>MAC (%)</th>
<th>( \lambda ) (oil:gas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>104</td>
<td>1.4</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.7</td>
<td>98</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>98</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.75</td>
<td>224</td>
</tr>
<tr>
<td>Methoxufluorane</td>
<td>0.16</td>
<td>960</td>
</tr>
</tbody>
</table>

The potency of an anesthetic increases as its liposolubility increases.
Halothane

First practical anesthetist, Widely used Non flammable , Non toxic , Sweet odor . Complete anesthetist only in high doses .

Direct depression of the myocardium, decrease BP. Sensitizes the myocardium to CA causing arrhythmias Reduces ventilatory response to carbon dioxide Produce adequate muscle relaxation Cardiotoxic, Hepatotoxic but not Nephrotoxic Repeated use may produce halothane hepatitis & malignant hyperthermia.
Enflurane

Mild stimulation of salivation & bronchial secretion. Myocardial depression similar to that of halothane. Sensitizes the myocardium to the effect of CA. Muscle relaxation is greater than that of halothane. CNS irritability in high doses, contraindicated in seizure disorder.

Releases free fluoride radical so it is contraindicated in patient with renal disorder. Cadiotoxic, Nephrotoxic but not Hepatotoxic.
Isoflurane

Most popular.

**Does not sensitize the myocardium to CA.**

Cerebral blood flow is increased while the cerebral metabolism is reduced

Produce adequate muscle relaxation

Less nephrotoxic & hepatotoxic than halothane

Agent of choice for **cardiac surgery**

Non Cardiotoxic, non Hepatotoxic, non Nephrotoxic
Methoxyflurane

Clear, colorless liquid with sweet fruity odor
Non flammable and non explosive in air
Most potent, high blood solubility, slow induction and recovery.

Respiratory and cardiovascular depression is generally similar to that of halothane
Sensitize the myocardium to CA.

Most toxic of the inhalational anesthetic
Cardiotoxic, Hepatotoxic, and Nephrotoxic
Desflurane
Rapid onset & recovery.
Differs from isoflurane only by substitution of a fluoride atom from chlorine
Produce a dose related decrease in blood pressure and cardiac output
Non Cardiotoxic, non Hepatotoxic, non Nephrotoxic

Sevoflurane
Rapid onset & recovery.
A fluorinated methyl ethyl ether
not irritating to the airways
Cardivascular effect is similar to isoflurane
Non Hologenated Ether
First anesthetic discovered
Seldom use today because of its flammability and explosive property
Irritant, pungent smell, increase bronchial secretion.
Chloroform
No longer use today because of liver toxicity
non explosive and non flammable
has rapid induction and recovery
Gaseous Anesthetics

Nitrous Oxide N2O (laughing gas) 1772

Sweet smelling, non irritating gas

Potent analgesic but a weak anesthetic, MAC 105

NO decrease in BP or COP & respirations is maintained

N2O 25% produces its maximum analgesic effect & as effectively as with a therapeutic dose of morphine.

N2O 25% is used in dentistry & to relieve pain of labor.

Low Tissue solubility, so it has a rapid onset, & recovery

The most common use of N2O is in combination with the more potent volatile anesthetics.

E.g. N2O 40% and halothane 0.5%

With this combination anesthesia is adequate for major surgery, and the cardiac effects of halothane are reduced.
Intravenous anesthetics.

Very lipid soluble.
Rapid onset (Seconds)
Rapid Awakening (Minutes)
Redistribution determines duration of action.
Slowly metabolized.

Ideally suitable for Induction.
Maintenance of short procedures.
In combination.
Supplement inhalational anesthesia.

Thiopental
Propofol

Most popular IV anesthetic, replaced thiopental.
Not analgesic but lowers dose of opioid needed.
Formulated as an emulsion, pain at injection site.

**Mechanism** is through potentiation **GABA**
Rapid onset (50 sec) & recovery in 4 to 8 min, by redistribution & rapid metabolism by the liver & extrahepatic tissues.
Anti-emetic, better postoperative period.
Potent respiratory depressant & cause marked decrease in **blood pressure** during induction.

The most common uses:
1- induction.
2- maintenance of anesthesia (infusion)
3- balanced anesthesia with volatile anesthetics, nitrous oxide, sedative-hypnotics, and opioids.
4- sedation of ventilated patients in the ICU
5- sedation during procedures
Barbiturates

Largely replaced by propofol.

Mechanism: activation of the GABA receptor.

They do not produce analgesia. Patients may react to painful stimuli but Unaware, Do not remember.

Direct negative inotropic effects on the heart. Compensatory increases in heart rate limit the decrease in BP.

Barbiturates are respiratory depressants.

Weak acids, can precipitate if given in an artery.
Slower acting drugs

- Benzodiazepines = Diazepam, Lorazepam, Midazolam
- Dissociative-anaesthetics = Ketamine
- Opioids analgesia = Fentanyl
Benzodiazepines
Most commonly used for preoperative medication, IV sedation, and suppression of seizure activity.

**Diazepam**, viscous, pain, Sedation

**Lorazepam**, long t½, viscous, pain. Sedation

**Midazolam**, aqueous, t½ 2hrs. Induction & Sedation,

**Flumazenil** antidote for overdose.

Midazolam is the only one of the benzodiazepine suitable for continuous infusion.

**midazolam** produces a greater decrease in systemic BP than **diazepam**, due to peripheral vasodilation.

transient apnea may follow rapid IV of **midazolam**

Pain during IV & IM injection are most pronounced with **diazepam**.
Ketamine

Produces "dissociative anesthesia," eyes remain open pupils are moderately dilated with a slow nystagmic gaze. **Mechanism**: inhibition of NMDA receptor complex. **Termination** by redistribution

Reflexes are preserved.

Increase lacrimation & salivation, increase IOP (Glaucoma) Evokes excitation, hallucination, fear and confusion, as the patient emerges from anesthesia.

Children have less severe emergence reactions.

Produces **profound analgesia**, transient increases in BP, HR, and COP, bronchodilation.

Given by IV, IM, oral, rectal, useful for uncooperative patients. Useful to produce analgesia in the early postoperative period
Opioid Analgesics
Morphine   Meperidine   Fentanyl
No amnesia, even with high doses of opioid. Routinely used for postoperative analgesia and as part of a balanced anesthesia. Opioids in large doses are used with large doses of benzodiazepines to achieve general anesthesia, in patients with limited circulatory reserve who undergo cardiac surgery.

Preanesthetic Medications
"Premedication"

Opioids
Benzodiazepines
Antimuscarinics
Antihistamines
Antiemetics
Glaucoma
Glaucoma:
Caused by raised ocular pressur (IOP). Without treatment, glaucoma results in damage to the retina and optic nerve, and eventually blindness.
Glaucoma is the third leading cause of blindness.
The balance between production and drainage of aqueous humor determines the intraocular pressure.
Normal IOP is 15.5 mmHg
Ciliary's processes is the site of manufacture of the aqueous humor physiologically activated by cAMP.

Outflow of aqueous humor:
1- filtration angle → trabecular meshwork →
   Canal of Schlemm (85%-95%)
2- Uveoscleral outflow (5%–15% aqueous passage from the anterior chamber into the ciliary muscle and then into the supraciliary & suprachoroidal spaces. The fluid then exits the eye through the intact sclera or along the nerves & the vessels that penetrate it.
Classification

**Primary glaucoma:**
- Open angle glaucoma
- Closed (narrow) angle glaucoma

**Secondary glaucoma**
Caused by complications of medications, trauma, infection, etc.

**Congenital glaucoma**
Childhood glaucoma usually detected during a baby’s first 6 months. It’s due to a fault in the development of the trabecular meshwork and surgery is the most effective treatment.
Open Angle Glaucoma

chronic simple or wide angle glaucoma

The most common type. Due to obstruction in the trabeculare meshwork. A chronic condition, treatment is pharmacologic.
Close angle glaucoma (acute or narrow angle) occurs in small eyes with shallow anterior chambers. A dilated iris can occlude the outflow drainage pathway. Acute and painful increases of pressure must be controlled on an emergency basis with drugs or by surgical removal of part of the iris.
Mechanisms of Action

1- reduction of aqueous humor secretion. β Blockers, Epinephrine Carbonic anhydrase inhibitors

2- enhancement of aqueous out-flow. a- Tubecular outflow, Cholinomimetics (Miotics) b- Uvescleral outflow Prostaglandin F2 analogs Epinephrine. Alpha2 agonists
Treatment

1- Cholinomimetics, Pilocarpine
2- α Agonists, Epinephrine
   α 2 agonists. Apraclonidine, brimonidine
3- β blockers Timolol, Betaxolol
4- Prostaglandin F2 analogs. Latanoprost
5- Diuretics, Carbonic anhydrase inhibitors
   Dorzolamide 2%, acetazolamide (Oral).

In open angle glaucoma, prostaglandin analogs & β blockers are the most popular because of convenience (once- or twice-daily dosing) & relative lack of adverse effects.

In acute closed-angle glaucoma cholinomimetics, acetazolamide, and osmotic agents are used before surgery. Other agents are too slow in this situation