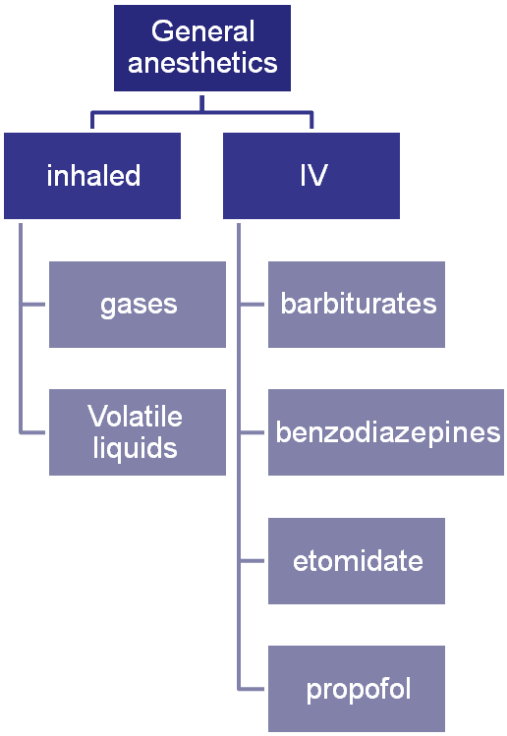
General anesthetics

Goals of surgical anesthesia:

Anesthesia decreases pain which causes:

- Muscle reflexes
- Suffering
- Autonomic reflexes



There are three terms you have to know before studying anesthetics:

Induction: The time taken from the administration of an anesthetic agent to the occurrence of loss of consciousness.

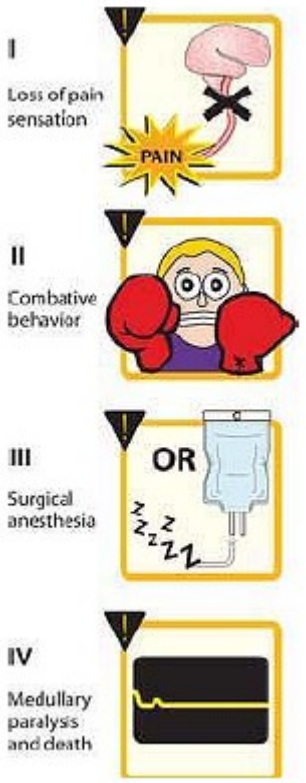
Maintenance: The effect of maintaining the state of anesthesia after the occurrence of induction

Recovery: The time taken to regain consciousness after discontinuing an anesthetic agent

Stages of anesthesia:

1. Stage of analgesia: the patient initially experiences analgesia. Later at this stage, analgesia and amnesia are experienced .
2. Stage of excitement: during this stage, the patient often appears to be delirious and may vocalize but is definitely amnesic. Respiration is irregular both in volume and rate, and retching and vomiting may occur if the patient is stimulated.
3. Stage of surgical anesthesia: begins with the recurrence of regular respiration and extends to complete cessation of spontaneous respiration (apnea).

- ↓Eye reflexes →movement seizes, pupil fixed



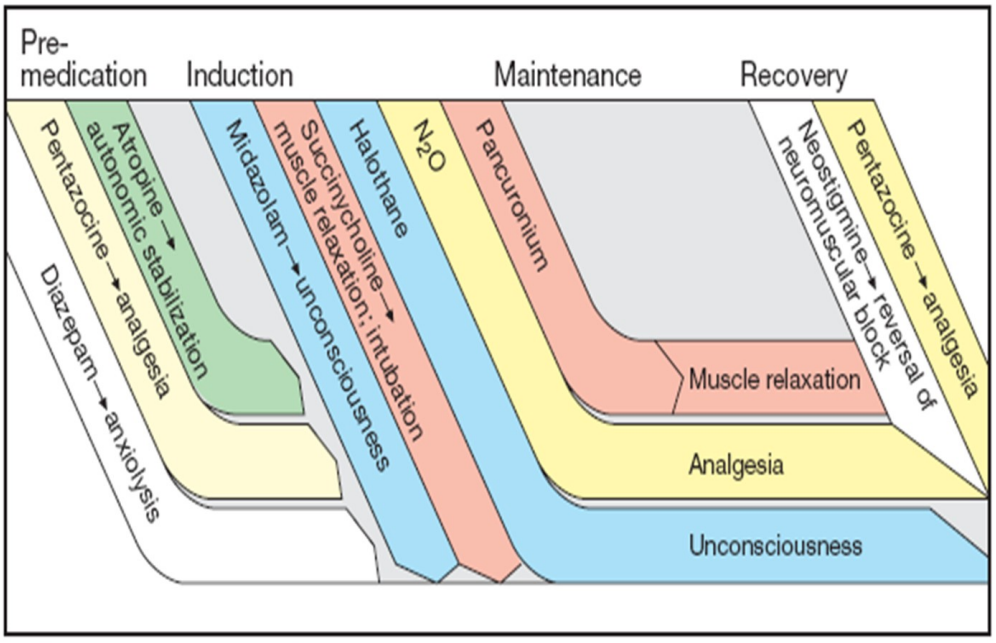
4. Stage of medullary depression: severe depression of the CNS, including the vasomotor center in the medulla, as well as the respiratory center in the brain stem, death rapidly occurs.

Multiple Adjunct Medication

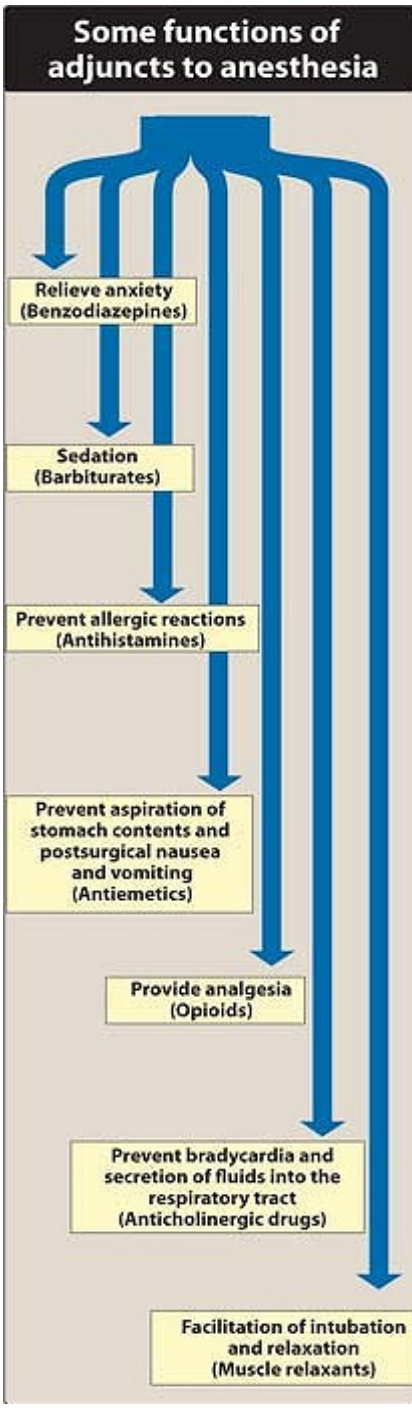
- Anticholinergic: for their amnesic effect, to prevent bradycardia and fluid secretion
- Antiemetics: to prevent aspiration of stomach content
- Antihistamines: to prevent allergic reactions
- Ranitidine: to reduce gastric acidity

Balanced Anesthesia:

The use of a combination of inhaled and IV agents. Similarly, muscle relaxant and local anesthetics are also used in balanced anesthesia. In addition, opioid analgesics and cardiovascular drugs are used to control autonomic reflexes.



C. Regimen for balanced anesthesia



Mechanism of action:

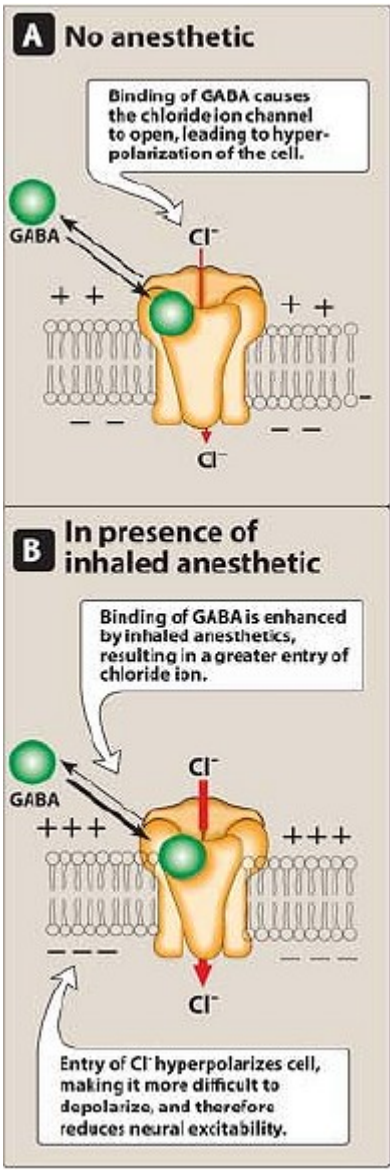
Old theory (Meyer—Overton):

- This theory states that there is a correlation between lipid solubility and the potency of the drug.
- Dissolution of the drug in the cell membrane may cause membrane dysfunction by membrane expansion or increased membrane fluidity

Newer theories:

- Anesthetics work by inhibiting the function of excitatory receptors e.g. Ach, glutamate, 5-HT and/or enhancing the inhibitory action of GABA or glycine.

- Some anesthetics work by opening K^+ channels causing cell hyperpolarization.



Anesthetics effect on systems and organs:

⇐ 1-Effects on the nervous system:

- Anesthetics inhibit synaptic transmission by inhibiting transmitter release resulting in the reduction of postsynaptic response.
- The most sensitive region in the brain to pain and other sensations is the **thalamic sensory nuclei and the deep layer of the cortex**. Anesthetics cause lack of awareness of sensory input (analgesia + amnesia).
- They interfere with the hippocampus which leads to short term amnesia.
- They decrease metabolic rate of the brain
- They increase cerebral blood flow which leads to increase in intracranial pressure. Anesthetic agents causing an increase in the intracranial pressure should be avoided in patients with head traumas or brain tumors.
- A depressing effect on the EEG.

⇐ 2-Effects on the cardiovascular system:

- They produce a decrease in the mean arterial pressure (MAP), either by depressing the cardiac output or by decreasing the systemic vascular resistance, which results in a decrease in cardiac oxygen demand.

⇐ 3- Effects on the respiratory system:

- With the exception of nitrous oxide (N_2O) and ketamine, all anesthetics depress respiration. This will lead to an increase in $PaCO_2$
- Lowering of the mucociliary movement leading to the pooling of secretions in the lung and development of alveolar atelectasis and lung infection.

⇐ 4-Effects on the liver:

- They decrease the hepatic blood flow by 15-40%

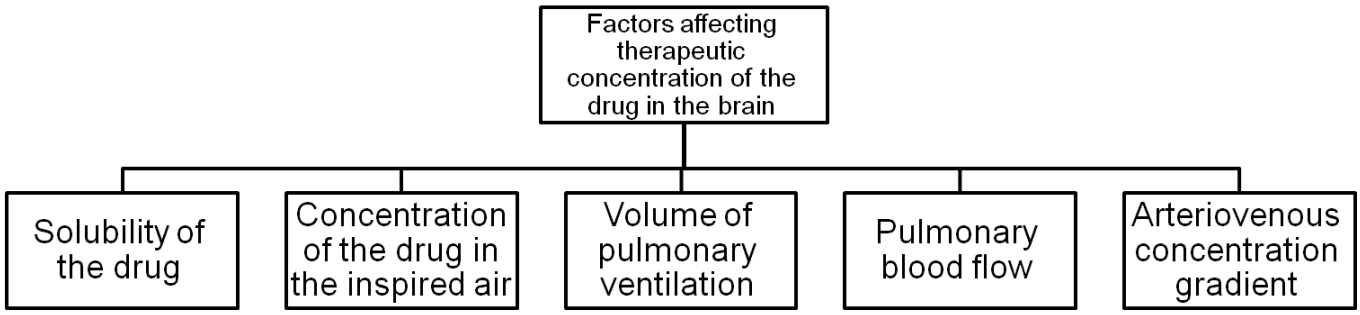
⇐ 5-Effects on the uterine musculature;

- All anesthetics, except for nitrous oxide, cause uterine muscle relaxation, and are used for intrauterine fetal manipulation.

Inhaled Anesthetics

Pharmacokinetics:

- The anesthetic agent has to move from the inspired air to the blood through the lung then the blood will deliver it to the brain.
- **Partial pressure (**or **tension): the** concentration of an inhaled anesthetic in a mixture of gases.
- Partial pressure is the force that moves the anesthetic from one compartment to the other.
- We have 4 compartments: airway, alveoli, blood, and brain.
- Gases move between these compartments based on partial pressure gradient between them.
- When partial pressure is equal in all 4 compartments —> steady state
- The factors which affect equilibrium are:



A. Solubility:

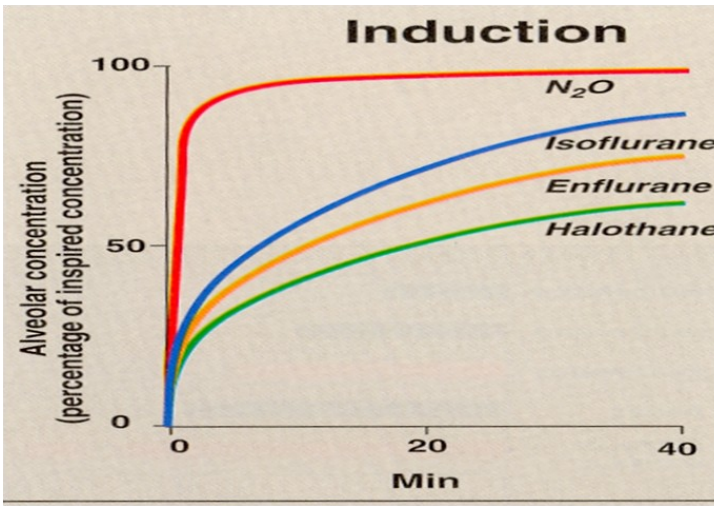
Blood:gas partition coefficient: the relative affinity of an anesthetic to dissolve in the blood compared with that of inspired gas.

- It has a direct proportion with solubility, the more solube drug, the higher blood:gas coefficient, the higher the affinity of the anesthetic for the blood.
- Let us take an example of a low-soluble anesthetic, nitrous oxide. First, when nitrous oxide moves from the lung to the blood, there is small distribution into the blood due to its low solubility, N_2O molecules coalesce and raise its partial pressure in the blood. Second, In this case the equilibrium between inhales anesthetic and arterial concentration will occur rapidly. This will lead to fast induction and recovery rate.

- Another example is of a high-soluble anesthetic, halothane. First, when it moves to the blood many molecules dissolve and are distributed causing a delay in the raise of partial pressure changes. This will lead to a slow induction and recovery rate.

-Solubility in fats:

- Oil:gas partition coefficient determines the potency of an anesthetic. The higher the lipid solubility is, the higher the onset of action at the CNS.
- However, high lipid solubility also delays the recovery from anesthesia due to the slow storing and release by low perfused tissues, mainly the adipose tissue. This effect is predominantly seen in obese patients exposed to repeated and prolonged amounts of anesthesia.



B. Anesthetic concentration in inspired air

The concentration of an inhaled anesthetic in the inspired gas mixture has a direct effect on both the maximum tension in the alveoli and the rate of the increase in its tension in arterial blood.

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C. Pulmonary ventilation:

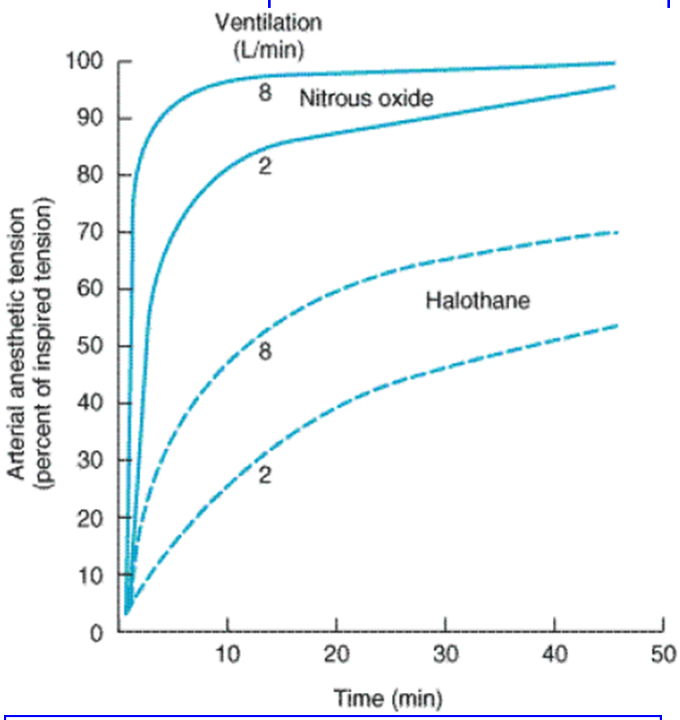
- The rate of rise of an anesthetic agent's partial pressure is directly dependent on both the rate and depth of ventilation.
- An increase in pulmonary ventilation will have the slight effect on anesthetics with low blood solubility (low blood:gas coefficient)
- An increase in pulmonary ventilation will significantly increase tension of agents with high blood solubility.

Anaesthetic	O /gas coefficient
Nitrous oxide	1.4
Halothane	224
Isoflurane	91
Enflurane	96
Diethyl ether	65

Oil:gas coefficient for some anesthetics

D. Pulmonary blood flow:

- An increase in pulmonary blood flow (cardiac output) will slow the rise of arterial tension:
  - ⇐ Increased pulmonary blood flow exposes larger volume of blood to the anesthetic.
  - ⇐ Thus, prolonged time for the anesthetic to dissolve in the blood; the anesthetic tension will rise slowly.
- ♦ A decrease in the blood flow has the opposite effect.
- ♦ This is applicable only to high-soluble anesthetics.



Effect of pulmonary ventilation (rise from 2 to 8L/min) on nitrous oxide and halothane

E. Arteriovenous Concentration Gradient:

- The amount of venous blood returning to the lungs may contain significantly less concentration of an anesthetic than in the arterial blood.
- The greater this difference in anesthetic gas tensions, the more time it will take to achieve equilibrium .

Anesthetic Potency:

- The potency of an anesthetic agent is measured for inhaled anesthetic by the minimum alveolar concentration (MAC).
- MAC is the anesthetic concentration that produces immobility in 50% of patients exposed to noxious stimulus (eg, surgical incision)
- The MAC value for nitrous oxide is more than 100%. That means we need 100% concentrated NO to produce 1 MAC. (the least potent anesthetic)

1- Inhaled Anesthetics

Halothane

- Non explosive, nonirritant, induction & recovery *relatively* fast. Highly potentPreferred in asthmatic patients because it dilates the bronchi.
- **Adverse effects:**
  - It sensitizes the heart to catecholamines → ventricular arrhythmias
  - Decreases cardiac output, Reversible reduction of GFR, Malignant hyperthermia results from excessive heat production in skeletal muscles due to the release of Ca^{++} from the sarcoplasmic reticulum→ rise in body temperature & muscle rigidity. Hepatotoxicity: halothane is metabolized to trifluoroacetic acid (Chlorotrifluroethyl) which reacts covalently with many proteins, mechanism thought to involve an immune response to certain fluroacetyl liver enzymes.

Nitrous oxide (non volatile gas)

- Odorless gas with rapid action, effective analgesic, used to reduce pain during childbirth
- Has low potency, at its highest normal concentration [80%] does not cause surgical anesthesia. Not used alone due to its low potency, yet it is used as an adjunct to volatile anesthetics.

Therapeutic uses:

- Outpatient anesthesia like in dental procedures, balanced anesthesia, neuroleptanalgesia, and during delivery due to the lack of uterine contraction caused by N_2O.

Adverse effects:

- Diffusion hypoxia.
- Postoperative nausea and vomiting
- Prolonged exposure causes inactivation of methionine synthase→ bone marrow depression, megaloblastic anemia. Leukopenia could also happen.
- Suspected to be a cause of increased frequency abortion & fetal abnormality among operating theatre staff**.**

Sevoflurane

- Has a better smell, and is less potent than halothane
- Rapid onset and recovery (Low blood solubility)
- Less metabolized (3- 5% to fluoride)
- Preferred in asthmatic patients

Adverse effects:

- Sevoflurane is degraded by the CO_2 in the anesthesia machines which leads to the formation of compound A causing proximal tubular necrosis. Decreases venous return

Enflurane

- Halogenated ether .Similar to halothane
- Substituted methoxyfluorane which is severly nephrotoxic, pungent, and might elicit breath holding (especially in children) (especially in children) which delays induction —> Not advised for use in children

Adverse effects:

- May cause seizures (contraindicated)
- Can induce malignant hyperthermia
- Decreases cardiac output
- Respiratory irritation **Contraindicated in renal failure because it's metabolized to fluorine which is nephrotoxic.**

Isoflurane

- It is now considered the most widely used volatile anesthetic.
- Not appreciably metabolized, little signs of toxicity with no proconvulsive activity
- Expensive
- Pungent
- Causes reflex tachycardia (sensitize the heart to catecholamines=halothane)
- Decreases venous return.

Comparative pharmacology of inhaled vapor anesthetics

	Halothane	Isoflurane	Sevoflurane	Desflurane
MAC	105%	1.2%	2%	6%
Respiratory irritation during inhaled induction	-	+	-	++
Heart rate	↓	↑↑	↑	↑↑
Blood pressure	↓	↓	↓	↓
Systemic vascular resistance	-	↓	↓	↓
Myocardial contractility	↓	-	-	-
Cardiac output	↓	-	-	-
Blood:gas partition coefficient*	2.5	1.5	0.69	0.42
Speed of onset (and recovery)	Slow	Medium	Rapid	Rapid
Metabolism	20%	0.2%	>2% (to fluoride)	<0.02%
Risk of 'hepatitis'	1:10,000?	Rare	Rare	Rare

*Blood:gas partition coefficient reflects solubility; higher numbers indicate higher solubility in blood relative to gas.

This is wrong it's 75%

2-Intravenous Anesthetics

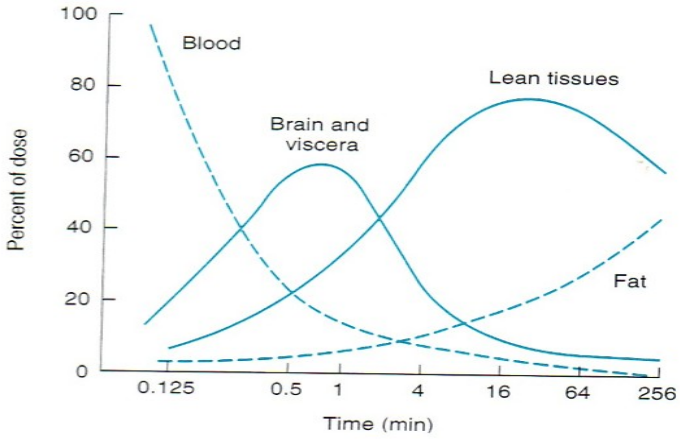
- Include thiopental, propfol, opioids, etomidate, and ketamine.
- All IV GA have no analgesic properties except for ketamine and opioids.
- Produce unconsciousness within 20 seconds.
- Can be used alone in short operations (total IV anesthesia).
- There is no need for skilled personnel or specialized vaporizer equipments, in contrast to inhaled GA.
- The benzodiazepines eg, diazepam & midazolam act less rapidly.
- Ketamine has a short period which is sufficient for its use in short (ambulatory) operations.
- Neuroleptanalgesia is produced by droperidol (an antipsychotic drug) + fentanyl (an opioid).

Barbiturates: thiopental

- High-lipid solubility
- Blood concentration declines rapidly due to the redistribution to tissues with large blood flow then to muscles, then it declines slowly due to its uptake by fats.
- It binds to plasma albumin [70%].

Adverse effects:

- Has no analgesic effect and can cause profound respiratory depression, tissue necrosis and ulceration if accidently injected around veins [treated by injection with procaine].
- CNS: ↓ICP, decreases brain metabolism and O2 utilization. Thus, it is used in head injuries and brain tumors.
- CVS: Hypotension & dysrhythmia.
- Can precipitate acute porphyria in susceptible individuals by inducing the production of α Aminolevulinic acid (ALA)



Benzodiazepines

- Midazolam, Diazepam, and Lorazepam
- Midazolam is preferred for GA use, with a relative rapid onset of action and better parenteral administration.
- Benzodiazepines have amnesic action, sedative, anxyiolysis and are considered the agents of choice for GA premedications. Midazolam is usually used right before a patient enters the operation room.
- They have no analgesic activity

Clinical uses

- Induction of general anesthesia.
- Alone in minor procedure (endoscopy).
- Balanced anesthesia (Midazolam).

Side effects

- Slow induction & recovery
- Respiratory depression

Etomidate

- Etomidate causes rapid loss of consciousness and is associated with less cardiovascular and respiratory depression.
- More rapidly metabolized than thiopental —>less drug redistribution to adipose tissue —> less long-hangover.

Clinical use

Etomidate is used for induction of anesthesia in patients with limited cardiovascular reserve such as elderly patients or patients in shock.

Side effects:

- Causes involuntary movements during induction & postoperative nausea & vomiting .
- Prolonged use →suppression of adrenal cortex →↑incidence of death in very old people.
- Pain at site of injection
- Teratogenic

Propofol

- Similar to thiopental in the rate of onset, yet propofol has a shorter recovery period

Pharmacokinetics:

- Rapidly metabolized, giving rapid recovery without the hangover effect.
- Short duration of action.
- Rapidly metabolized in liver
- Post administration distribution $t_{1/2}$= 2-8 minutes; redistribution $t_{1/2}$= 30-60 minutes

Advantages:

- Decreases ICP
- Antiemetic action and feeling of well-being after recovery.

Clinical use

Could be used as a continuous infusion to maintain surgical anesthesia

Side effects:

- Hypotension (mainly by marked decrease in PVR).
- Excitation (involuntary movements).
- Pain at the site of injection.
- Expensive
- Propofol is prepared in an emulsified formula for the sake of administration. This lipid formula might cause an increase in serum lipid levels. Likewise, this formula provides a suitable media for bacterial infection before drug administration. Therefore, nowadays, Ethylenediaminetetraacetic acid (EDTA) is given prophylactically.

Ketamine

- It resembles phencyclidine.
- Produces anesthesia–like state & analgesia.
- Ketamine is the only IV GA which has both analgesic and anesthetic properties.

Mechanism of action

It blocks glutamate's excitatory action at its receptor NMDA.

Pharmacokinetics

Onset 2-3min, producing dissociative anesthesia (a marked sensory loss, analgesia, paralysis of movment & amnesia *without* actual loss of consciousness).

Clinical uses:

- Minor operations (children, elderly, shock patients) .
- Short duration diagnostic procedures

Advantages:

- Can be given IV, IM (IM is good for children).
- No bronchospasm.
- Longer duration of action than thiopental.
- Hypovolemic or shock patients.

Side effects:

- Post operative hallucination (less marked in children)
- Risk of hypertension cerebral hemorrhage.
- Raises the ICP which might result in cerebral hemorrhage
- During induction & recovery involuntary movements & peculiar sensory experience may occur.

Contraindications

- CVS diseases
- Head injuries

Opiate drugs
Fentanyl, Sufentanil, Alfentanil, Remifentanil

Fentanyl:

Potent analgesia.
No muscle relaxation

Pharmacokinetics:

Rapid onset and short duration of action

Clinical uses

- Cardiac surgery (morphine + nitrous oxide).
- Neuroleptanalgesia (Fentanyl + Droperidol).
- Neuroleptanesthesia (Fentanyl+Droperidol+ nitrous oxide).

Side effects

- Respiratory depression (bronchospasm) (wooden rigidity)
- Hypotension
- Nausea and vomiting
- Increase in ICP
- Prolongation of labor and fetal distress
- Urinary retention

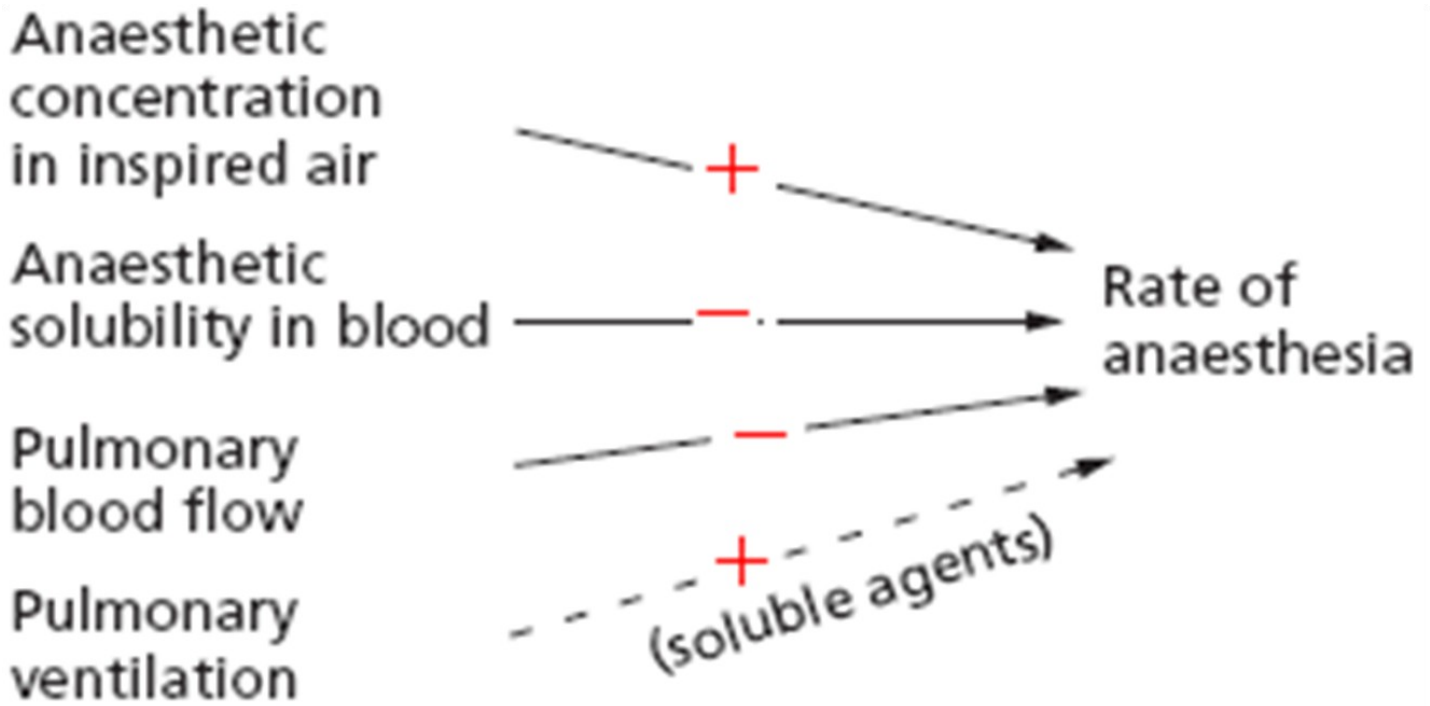
Contraindication

- Head injuries
- Pregnancy
- COPD
- Hypovolemic shock (large doses only)

Neuroleptanalgesia

- A state of analgesia & sedation & muscle relaxation BUT No loss of consciousness
- Contraindicated in parkinsonism.
- Diagnostic procedure that require cooperation of the patient.

A Summary of the Pharmacokinetics of Inhaled Anesthetics



Factors determining the onset of action of inhalational anaesthetics.