Medicinal Chemistry

Chapter 13 & 14

ANESTHETICS

Dr. Amin Thawabteh

Contents

General Anesthesia

General anesthesia (GA) is the state produced when a patient receives medications for amnesia, analgesia, muscle relaxation, and sedation. An anesthetized patient can be thought of as being in a controlled, reversible state of unconsciousness. General anesthetics depress the central nervous system to a sufficient degree to permit the performance of surgery and other noxious or unpleasant procedures.

General anesthesia uses intravenous and inhaled agents to allow adequate surgical access to the operative site. A point worth noting is that general anesthesia may not always be the best choice; depending on a patient's clinical presentation, local or regional anesthesia may be more appropriate.

General anesthesia is a reversible state of CNS depression, causing loss of response to and perception of stimuli.

For patients undergoing surgical or medical procedures, anesthesia provides five important benefits:

- Sedation and reduced anxiety
- Lack of awareness and amnesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes
- Analgesia

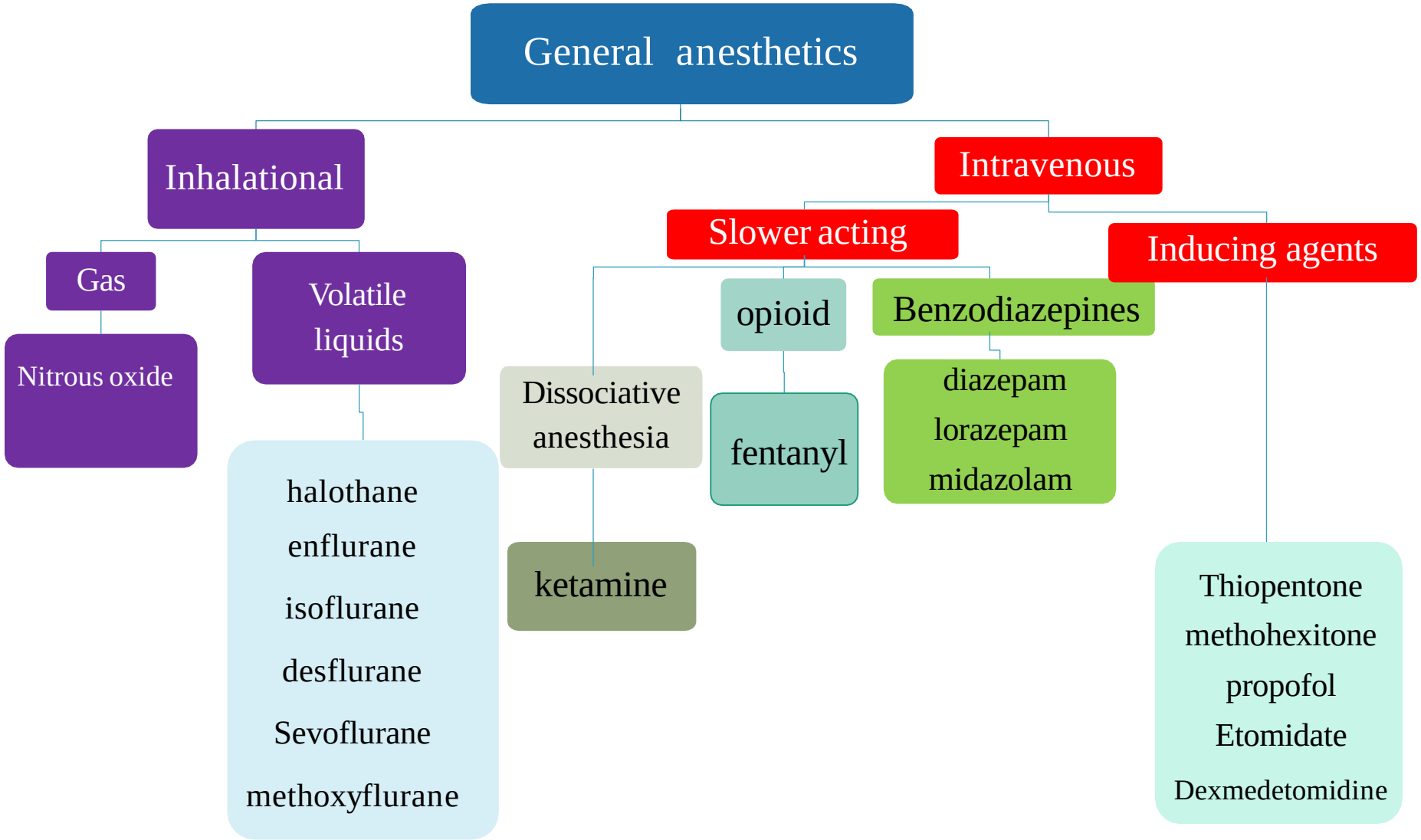
Because no single agent provides all desirable properties both rapidly and safely, several categories of drugs are combined (I.V and inhaled anesthesia and preanesthetic medications) to produce optimal anesthesia known as a **Balanced anesthesia.**

Patient factors in selection of anesthesia

Drugs are chosen to provide safe and efficient anesthesia based on:

1. The type of the surgical or diagnostic procedure
2. Patient characteristics such as organ function, medical conditions, and concurrent medications. e.g., HTN, bronchial asthma.

CLASSIFICATION



Status of organ systems

Respiratory system:

All inhaled anesthetics depress the respiratory system. They are bronchodilators.

Liver and kidney:

The release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs, especially with repeated anesthetic administration over a short period of time.

Pregnancy:

Effects on fetal organogenesis are a major concern in early pregnancy.

1.Nitrous oxide can cause aplastic anemia in the unborn child. Oral clefts have occurred in the fetuses of women who have received benzodiazepines.

2.Diazepam should not be used routinely during labor, because it results in temporary hypotonia and altered thermoregulation in the newborn.

Nervous system:

- The existence of neurologic disorders (e.g., epilepsy or myasthenia gravis) influences the selection of anesthetic.
- A patient history of a genetically determined sensitivity to halogenated hydrocarbon-induced **malignant hyperthermia** "an autosomal dominant genetic disorder of skeletal muscle" that occurs in susceptible individuals undergoing general anesthesia with volatile agents and muscle relaxants (eg, succinylcholine).
- The malignant hyperthermia syndrome consists of the rapid onset of tachycardia and hypertension, severe muscle rigidity, hyperthermia
- Rx Dantroline

Preanesthetic Medications

Preanesthetic medications serve to

- calm the patient, relieve pain,
- protect against undesirable effects of the subsequently administered anesthetics or the surgical procedure.
- facilitate smooth induction of anesthesia,
- lowered the required dose of anesthetic

Preanesthetic Medicine:

- Benzodiazepines; midazolam or diazepam: Anxiolysis & amnesia.
- Diphenhydramine: Prevention of allergic reactions: antihistamines

- H2 receptor blocker- famotidine, ranitidine: Reduce gastric acidity.
- Antiemetics ondansetron: Prevents aspiration of stomach contents and post surgical vomiting:
- Acetaminophen or opioids (fentanyl) for analgesia
- Anticholinergics: (glycopyrrolate, scopolamine):
- Reduce bronchial and salivary secretion: irritant inhaled anesthetic cause excessive salivation and secretion.

Stages and depth of anesthesia

General anesthesia has three stages: induction, maintenance, and recovery.

Use preanesthetic medication

↓

Induce by I.V thiopental or suitable alternative

↓

Use muscle relaxant → Intubate

↓

Use, usually a mixture of N_2O and a halogenated hydrocarbon→ maintain and monitor.

↓

Withdraw the drugs → recover

Induction: The period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient. It depends on how fast effective concentrations of the anesthetic drug reach the brain.

Thus GA is normally induced with an I.V thiopental, which produces unconsciousness within 25 seconds or propofol producing unconsciousness in 30 to 40 seconds after injection.

At that time, additional inhalation or IV drugs may be given to produce the desired depth of surgical stage III anesthesia. This often includes an IV neuromuscular blocker such as rocuronium, vecuronium, or succinylcholine to facilitate tracheal intubation and muscle relaxation.

Maintenance: After administering the anesthetic, vital signs and response to stimuli are monitored continuously to balance the amount of drug inhaled and/or infused with the depth of anesthesia.

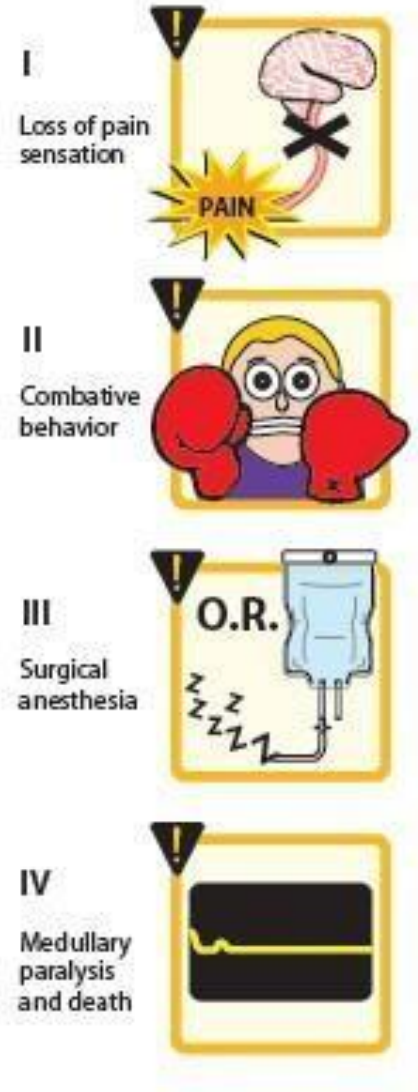
Maintenance is commonly provided with volatile anesthetics, which offer good control over the depth of anesthesia.

Recovery: The time from discontinuation of administration of the anesthesia until consciousness and protective physiologic reflexes are regained. It depends on how fast the anesthetic drug diffuses from the brain.

The patient is monitored to assure full recovery, with normal physiologic functions (spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, and no delayed reactions such as respiratory depression).

Depth of anesthesia

- Depth of anesthesia is the degree to which the CNS is depressed and is a useful parameter for individualizing anesthesia
  - Stage I Analgesia
  - Stage II Delirium
  - Stage III Surgical anesthesia
  - Stage IV Medullary paralysis



Stage I (Analgesia): The patient is conscious and experiences sensations of warmth, remoteness, drifting, falling, and giddiness. There is a marked reduction in the perception of painful stimuli. This stage is used often in obstetrics and minor surgery.

Stage II (Delirium): This stage begins with the loss of consciousness. Depression of higher centres produces a variety of effects including excitement, involuntary activity, and increased skeletal muscle tone and respiration.

Stage III (Surgical anaesthesia): This is the stage of unconsciousness and paralysis of reflexes. Respiration is regular and blood pressure is maintained. All surgical procedures are carried out in this stage.

Stage IV (Medullary paralysis): Respiratory and circulatory failures occur as depression of the vital centres of the medulla and brain stem occur.

Inhalation anesthetics

Inhaled gases are used primarily for maintenance of anesthesia.

Depth of anesthesia can be rapidly altered by changing the inhaled concentration.

Common features of inhaled anesthetics

- Modern inhalation anesthetics are nonflammable, nonexplosive agents.
- Decrease cerebrovascular resistance, resulting in increased perfusion of the brain
- Cause bronchodilation, and decrease both spontaneous ventilation and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, redirecting blood flow to more oxygenated regions).
- Movement of these agents from the lungs to various body compartments depends upon their solubility in blood and tissues, as well as on blood flow. These factors play a role in induction and recovery.

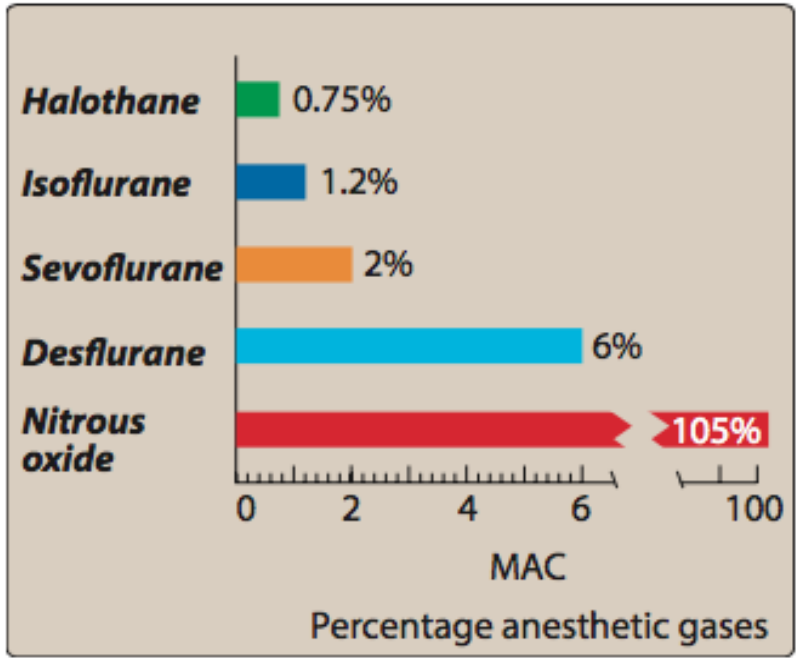
Minimum alveolar concentration

MAC (potency): is the concentration of a vapour in the alveoli of the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus.

- MAC is the ED_{50} of the anesthetic.

MAC expressed as the percentage of gas in a mixture required to achieve the effect.

Numerically, MAC is small for potent anesthetics such as sevoflurane and large for less potent agents such as nitrous oxide.



Uptake and distribution of inhalation anesthetics

- The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure (P_{br}) of inhaled anesthetic (partial pressure equilibrium between alveoli [P_{alv}] and brain [P_{br}]).

- Thus, the alveoli are the "windows to the brain" for inhaled anesthetics.

- The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force moving the anesthetic into the alveolar space and, thence, into the blood (P_a), which delivers the drug to the brain and other body compartments.

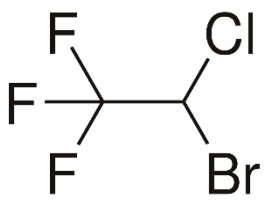
- Because gases move from one compartment to another within the body according to partial pressure gradients, a **steady state** (SS) is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture.

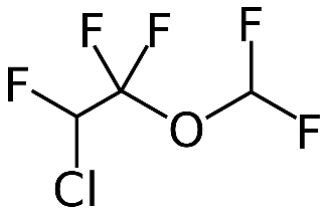
$$\mathbf{P_{alv} = P_a = P_b}$$

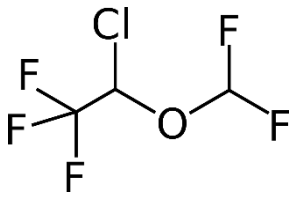
Factors Determine the time course for attaining Steady State:

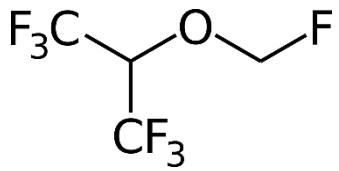
- Solubility in the blood: called the blood/gas partition coefficient.
- The solubility in blood is ranked in the following order:

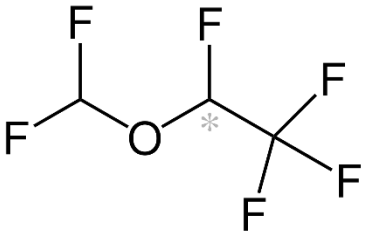
halothane>enflurane>isoflurane>sevoflurane>desflurane>N_2O.











- An inhalational anesthetic agent with low solubility in blood shows fast induction and also recovery time (e.g., N_2O), and an agent with relatively high solubility in blood shows slower induction and recovery time (e.g., halothane).

Effect of different tissue types on anesthetic uptake:

- It is also directly proportional to the capacity of that tissue to store anesthetic (a larger capacity results in a longer time required to achieve steady state).

- Capacity, in turn, is directly proportional to the tissue's volume and the tissue/ blood solubility coefficient of the anesthetic.

Four major tissue compartments determine the time course of anesthetic uptake:

a. **Brain, heart, liver, kidney, and endocrine glands:** these highly perfused tissues rapidly attain a SS

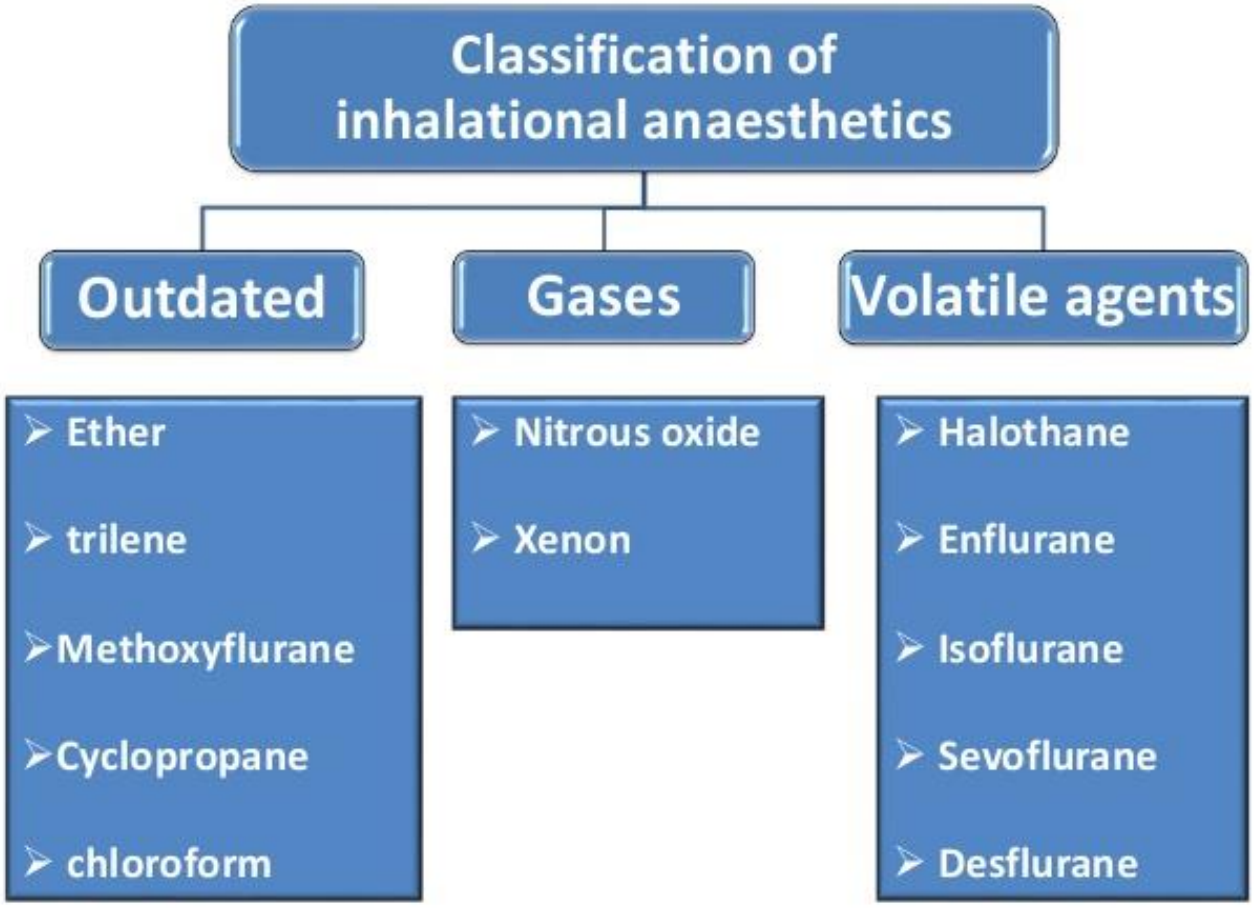
b. **Skeletal muscles:** poorly perfused, and have a large volume, prolong the time required to achieve SS

c. **Fat:** poorly perfused. However, potent GA are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. So slow delivery to a high capacity and prolongs the time required to achieve SS

d. **Bone, ligaments, and cartilage:** these are poorly perfused and have a relatively low capacity to store anesthetic.

The ideal should:

1. high margin of safety,
2. have rapid and pleasant induction and recovery,
3. be easily controlled and regulated,
4. have no side-effects or toxicity,
5. should not depress the cardiovascular and respiratory systems,
6. be non-flammable and non-explosive,
7. provide good analgesia and muscle relaxation,
8. and have low cost.



Mechanisms of anesthesia

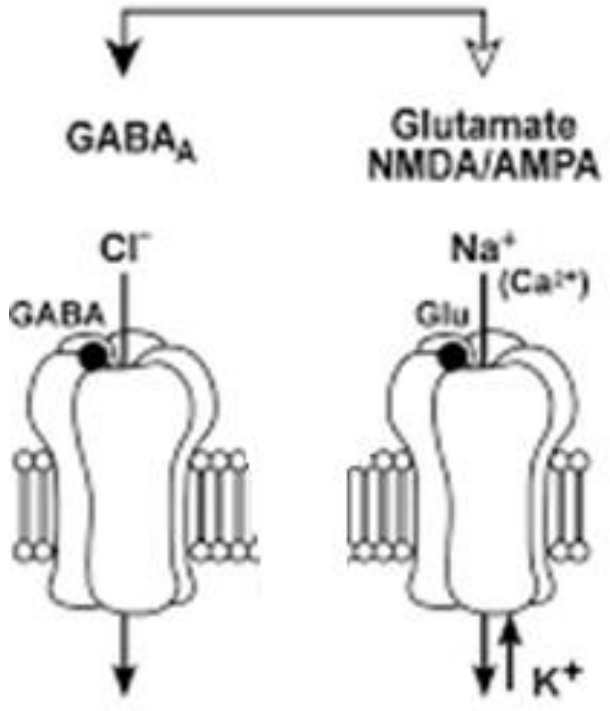
1-Blocking the NMDA and glutamate controlled channels.

Glutamate or NMDA (N-methyl-D-aspartate) receptors in the CNS are activated by the excitatory AA neurotransmitter glutamic acid. This activation opens the channel, allowing K^+ to flow to the extra cellular fluid and Na and Ca^{++} to flow into the nerve cell.

2- Activation of the inhibitory GABA receptor controlled channel.

Binding of GABA (inhibitory transmitter) to their receptors will open the Cl^- channel, leading to the influx of Cl^- and hyper- polarization of the neuron.

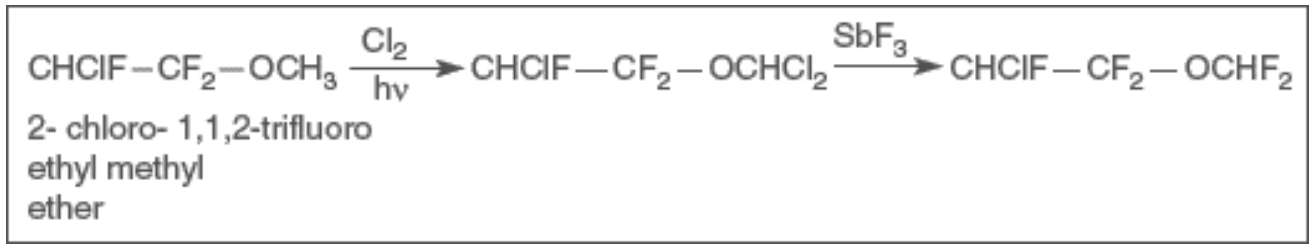
Halothane and isoflurane inhibit the synaptic destruction of GABA, thereby increasing the GABA-ergic neurotransmission.

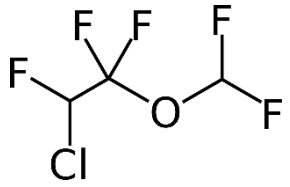


Enflurane

2-Chloro-1,1,2-trifluoroethyldifluoromethyl ether

***Synthesis*





Adv.
pleasant-smelling, non-flammable, halogenated ether anaesthetic that provides rapid induction with little or no excitement.

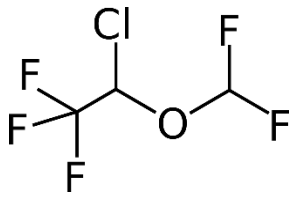
Dis. Adv.
high concentrations may cause CVS depression and CNS stimulation.

Dose:

Induction: 2.0%–4.5% in oxygen or with oxygen-nitrous oxide mixtures. Induction usually requires 7–10 minutes. Maintenance usually is accomplished with 0.5%–3% concentrations.

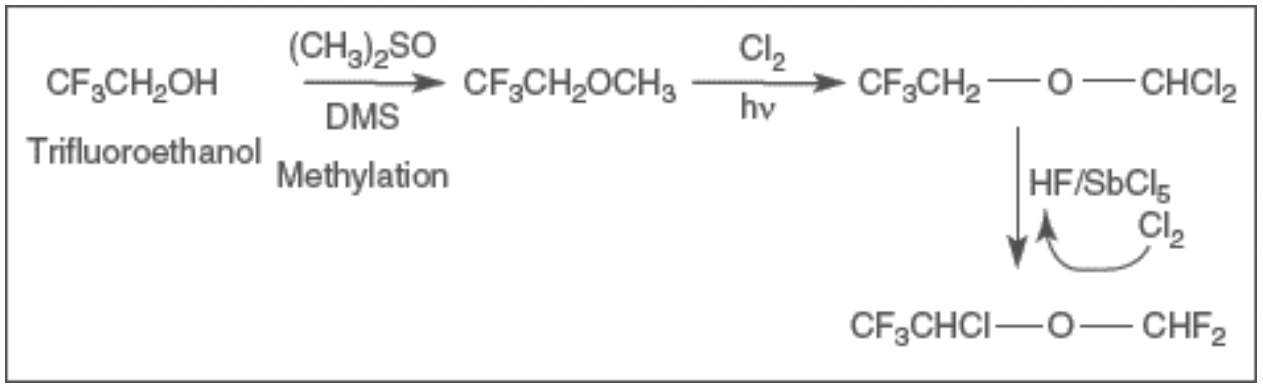
Isoflurane

1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether



***Synthesis*

Methylating the 2,2,2-trifluoro/ethanol by with dimethylsulphate



Uses:

Adv.
is a non-flammable inhalation anaesthetic for induction and maintenance of general anaesthesia. Induction of and recovery from isoflurane anaesthesia is rapid. Isoflurane is said to offer advantages over all available inhalation anaesthetics, especially in its lack of any important toxicity.

Dose:

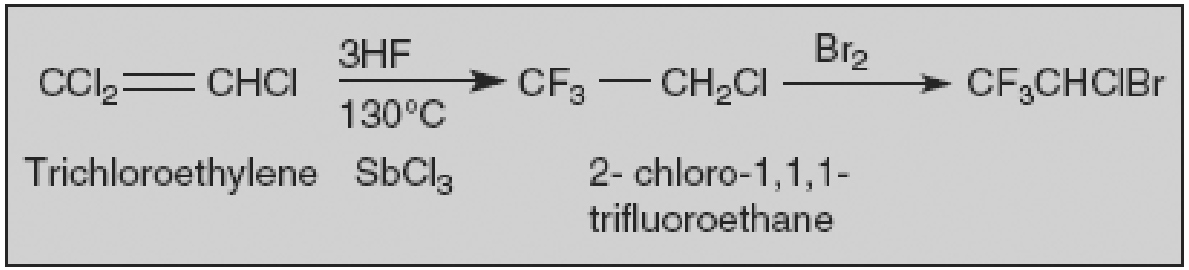
Induction: 1.5%–3.0% usually produce surgical anaesthesia in 7–10 minutes. Surgical levels of anaesthesia can be sustained with 1.0%–2.5% concentrations when nitrous oxide is used concomitantly.

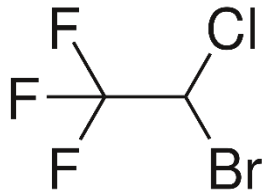
Halothane

2-Bromo-2-chloro-1,1,1- trifluoroethane

Synthesis

Addition of hydrogen fluoride to tricholoroethylene





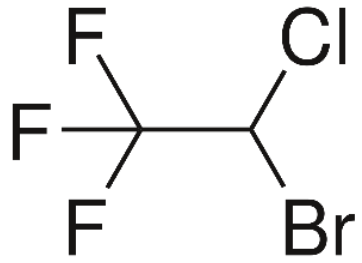
Uses:

Halothane is a potent, relatively safe, frequently employed general inhalation anaesthetic. Induction with halothane is smooth and rapid with little or no excitement. It is not a potent analgesic and skeletal muscle relaxant. Therefore, it is used frequently in conjunction with nitrous oxide and with succinylcholine, tubocurarine, or gallamine.

Dose:

For induction: 1.0%–4.0% vaporized by a flow of oxygen or nitrous oxide-oxygen mixture. For maintenance: 0.5%–1.5%.

Halothane



Advantages:

- Potent anesthetic, rapid induction &recovery
- Neither flammable nor explosive, sweet smell, non irritant
- Does not augment bronchial and salivary secretions.
- Low incidence of post operative nausea and vomiting.
- Relaxes both skeletal and uterine muscle, and can be used in obstetrics when uterine relaxation is indicated.
- Combined with its pleasant odor, this makes it suitable in children for inhalation induction.

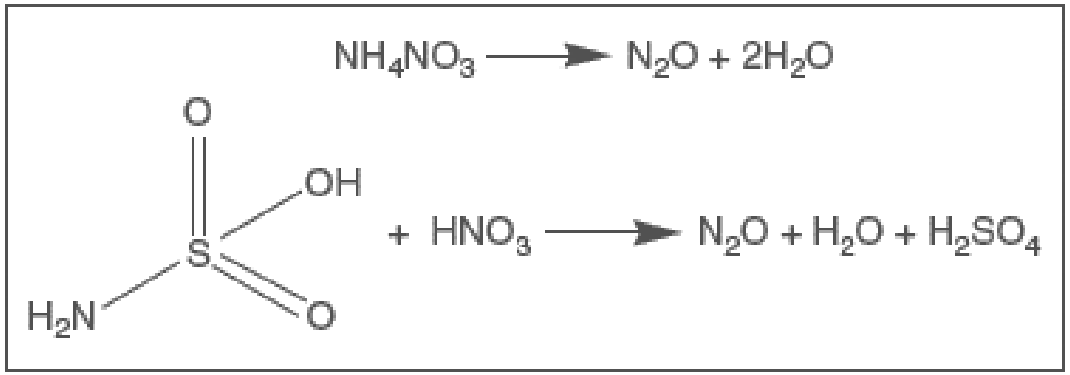
Disadvantages:

- Weak analgesic (thus is usually coadministerd with N_2O,opioids)
- Is a strong respiratory depressant
- Is a strong cardiovascular depressant; halothane is vagomimetic and cause atropine-sensitive bradycardia.
- Hepatotoxic: is oxidatively metabolized in the liver to tissuetoxic hydrocarbons (e.g., trifluroethanol and bromide ion).
- Malignant hyperthermia

Nitrous oxide

Synthesis

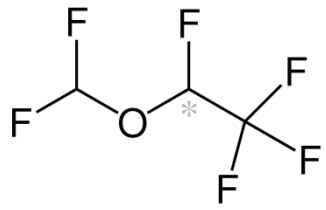
Thermal decomposition of ammonium nitrate



Dose: Analgesia: 25%–50%; maintenance: 30%–70%. Administered with at least 25%–30% oxygen

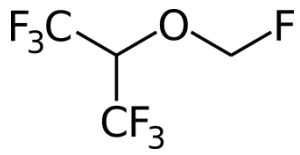
- ***It is a potent analgesic but a weak general anesthetic.***
- ***Rapid onset and recovery:***
- ***Does not depress respiration, and no muscle relaxation.***
- ***Clinical use: dental surgery, obstetrics, postoperative physiotherapy, refractory pain in terminal illness, and maintenance of anesthesia.***

Desflurane



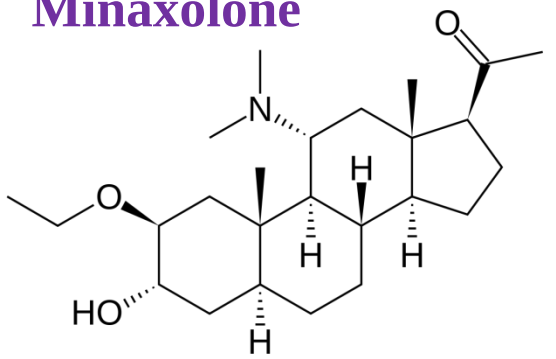
Used for maintenance of general ANA. Together with sevoflurane, it is gradually replacing isoflurane for human use. It has the most rapid onset and offset of the volatile ANA drugs used for general ANA due to its low solubility in blood.

Sevoflurane



It is a sweet-smelling, non-flammable, highly fluorinated methyl isopropyl ether used for induction and maintenance of general ANA. Together with desflurane, it is replacing isoflurane and halothane in modern anaesthesiology. It is often administered in a mixture of nitrous oxide and oxygen.

Minaxolone



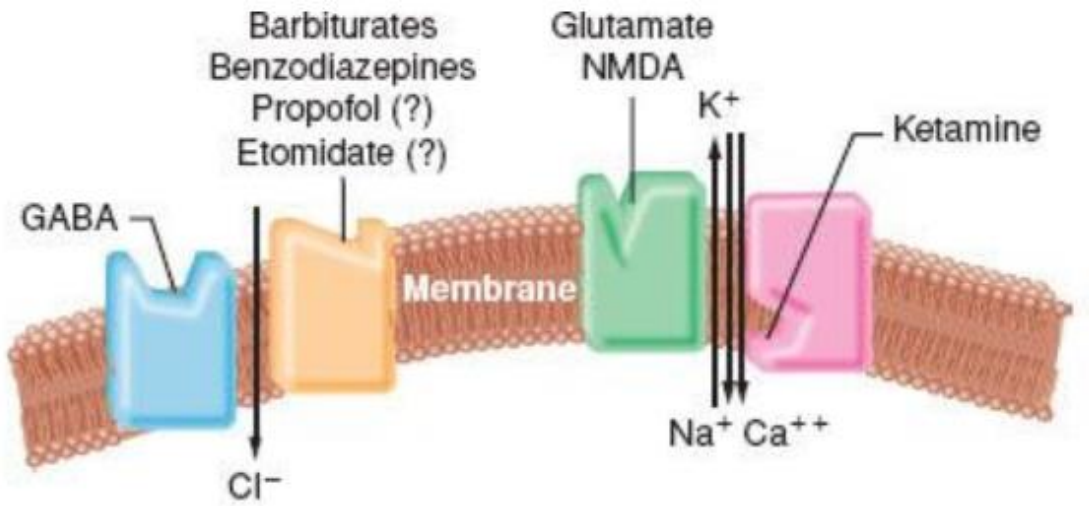
It is a new water-soluble steroid ANA, and it appears to be a safe and effective intravenous ANA with impressive recovery characteristics. Its only drawback would seem to be its high incidence of excitatory movements and hypertonus. It appears to be a promising intravenous anaesthetic agent worthy of further clinical investigation.

Intravenous Anesthetics

- Include:
  - Barbiturates
    - Thiopental & Methohexital
  - Opioids
    - Alfentanil, Meperidine, Fentanyl, Sufentanil (agonists)
    - Naloxone (antagonist)
  - Benzodiazepines
    - Diazepam, Midazolam
    - Flumazenil (antagonist)
  - Miscellaneous Agents
    - Etomidate – non-barbiturate hypnotic agent without analgesic properties
    - Droperidol - Neuroleptic (similar to Haloperidol) - combined with Fentanyl and is used for neuroleptanalgesia (state of analgesia and amnesia)
    - Ketamine - dissociative anesthetic
    - Propofol

General Uses of IV Anesthetics

- **Primary Use = induction of general anesthesia**
  - Supplement general anesthesia
  - maintain general anesthesia
  - provide sedation
  - control Blood Pressure

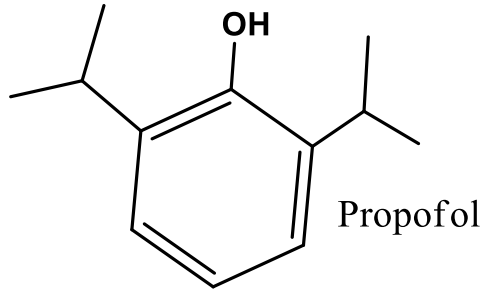


Mechanisms of Action

- Enhanced GABA effect on SABA Receptors: Etomidate, Barbiturates, Propofol, Benzodiazepines
- Activate K channels (hyperpolarize): ketamine, xenon
- Inhibit NMDA glutamate) receptors: ketamine, xenon, high dose barbiturates
- Inhibit synaptic proteins (reduce NT release) amnesia)
- Enhance glycine effect on glycine Rs (immobility)

Propofol (Deprivan)

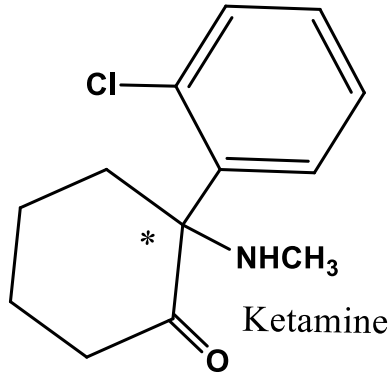
2,6-Di-isopropylphenol



- Propofol is a short acting anesthetic that act via enhancing the GABA-ergic neurotransmission in the CNS. It binds allosterically to GABA receptor at a site different from that of benzodiazepines. It achieves hypnosis in one minute & lasts for 5 minutes.
- Maintenance of anesthesia is achieved with volatile anesthetics or additional doses of it.
- It is formulated as 1 or 2% emulsion in soybean oil or glycerol.
- It is more, effective than thiopental. Rarely associated with vomiting.
- Metabolism proceeds rapidly via glucuronide and sulfate conjugation in liver.

Ketamine

2-(2-Chlorophenyl)-2-methylaminocyclohexanone



Ketamine

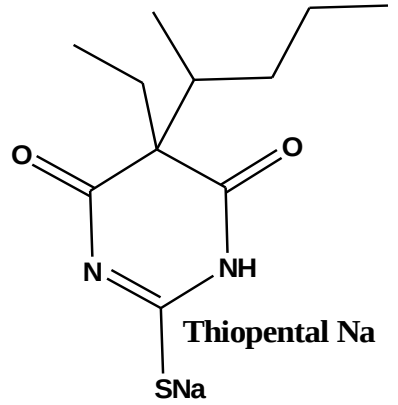
- Ketamine hydrochloride is a very potent, rapidly acting anesthetic agent.
- The S (+) ketamine is two to three times more potent than the R (-) ketamine as an analgesic.
- Its duration of action is relatively short (10-25 minutes).
- It produces anesthesia by blocking the NMDA controlled channels.

- ketamine is suitable for diagnostic purposes and for surgical procedures that do not require muscle relaxation.
- Patients older than 16 will often (27%) have wild dreams and hallucinations during emergence, that may last for 24 hours and so it is only indicated for children less than 16 years old.

Ultrashort-acting barbiturates:

A- Thiopental sodium

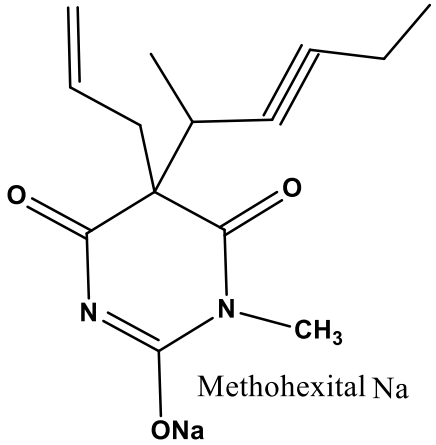
- Used to produce rapid unconsciousness for surgical and basal anesthesia (induce anesthesia).
The induction is very rapid. The long side chain substitution at position-5 is an essential feature for increasing lipid solubility and hence the rate of passing through the BBB.



Thiopental Na

- It is the most widely used ultrashort-acting barbiturate. The presence of sulfur in **thiopental** increases lipid solubility and facilitates its entry to the brain.
- Its short duration of action is due to partitioning from the brain into body fat. It is metabolized by oxidative desulphurization

B- Methohexital sodium

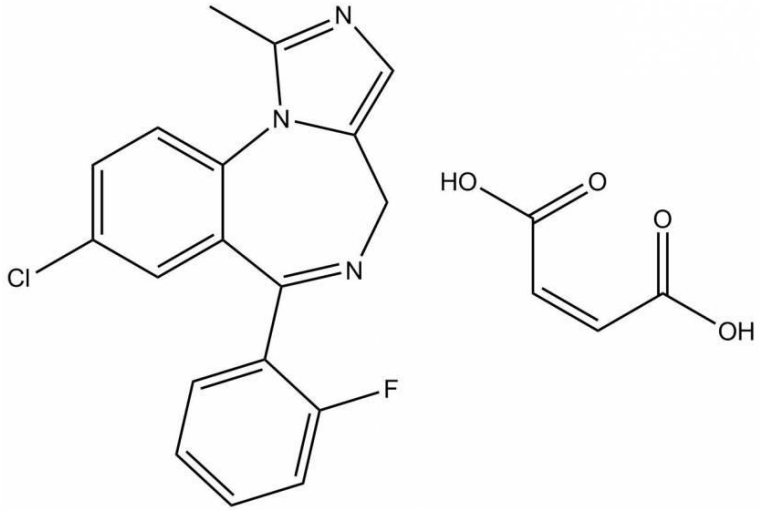


Methohexital Na

- It is N-methylated barbiturate that has pKa of 8.4, versus 7.6 for the non-methylated compound.
- This pKa value increases the concentration of the lipid-soluble free acid form at the physiological pH.
- N-methylation decreases duration of action.
- The compound also has extensive hydrophobic character because the long unsaturated side chains (9-Cs).
- Overall, it can rapidly penetrate the CNS after IV injection and then redistribute rapidly to other body sites and undergo rapid metabolic inactivation.
- Finally, it has an accessible site of metabolic inactivation, the CH_2 α to the triple bond.

Benzodiazepines

-Benzodiazepines alone can not produce surgical anesthesia. However, some benzodiazepines are used to induce anesthesia. e.g: Medazolam maleate



Adjuvant to general anesthesia

1.Narcotic analgesics: such as morphine and meperidine to reduce anxiety .

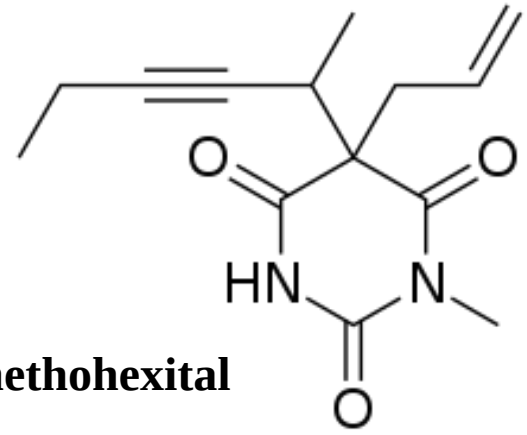
2.Sedatives: such as benzodiazepines, to produce sedation and reduce anxiety.

3.Anticholinergics: such as scopolamine, to inhibit excessive respiratory secretion.

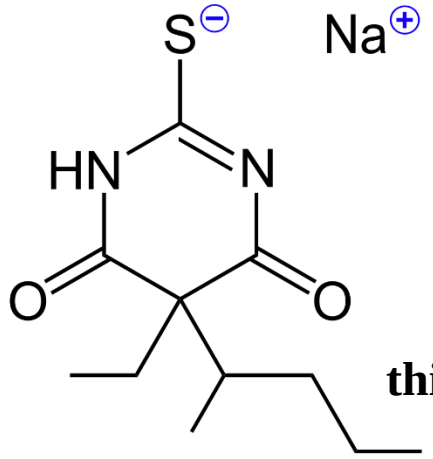
4.Skeletal muscle relaxants: such as succinylcholine and vencuronium to relax the muscles for optimum surgical working conditions.

Barbiturates (thiopental, methohexital)

- Potent anesthetic but a weak analgesic
- High lipid solubility; quickly enter the CNS and depress function, often in less than one minute, and redistribution occur very rapidly as well to other body tissues, including skeletal muscle and ultimately adipose tissue (serve as a reservoir).
- All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm



methohexital



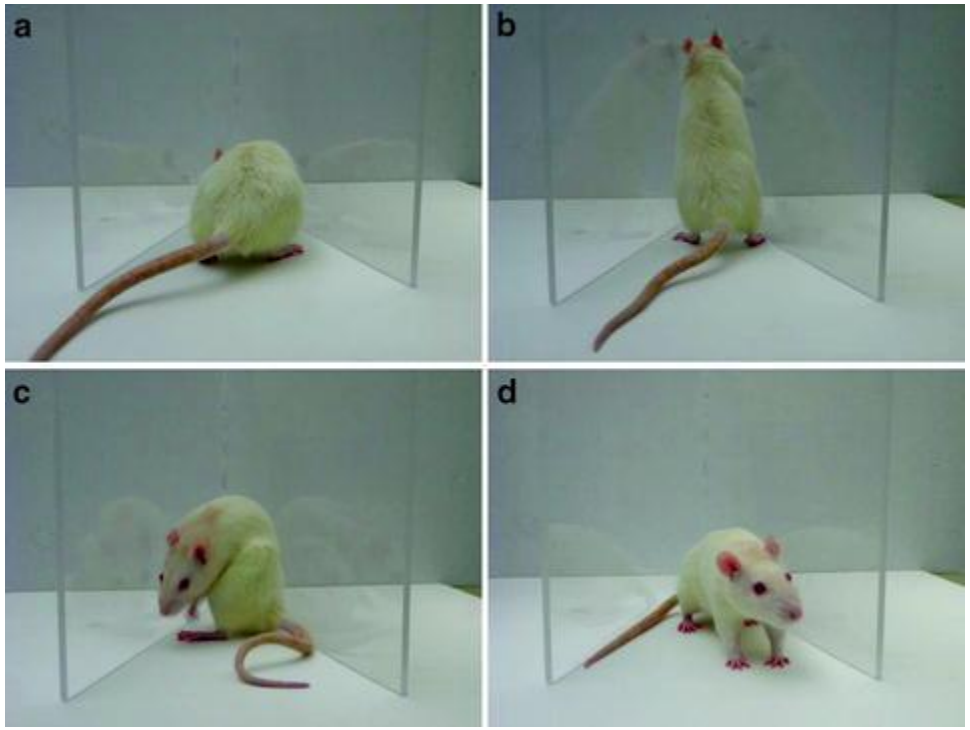
thiopental

Anesthetic Toxicity

The conventional view of general anesthesia is that anesthetics produce a reversible loss of consciousness and that CNS function returns to basal levels upon termination of anesthesia and recovery of consciousness.

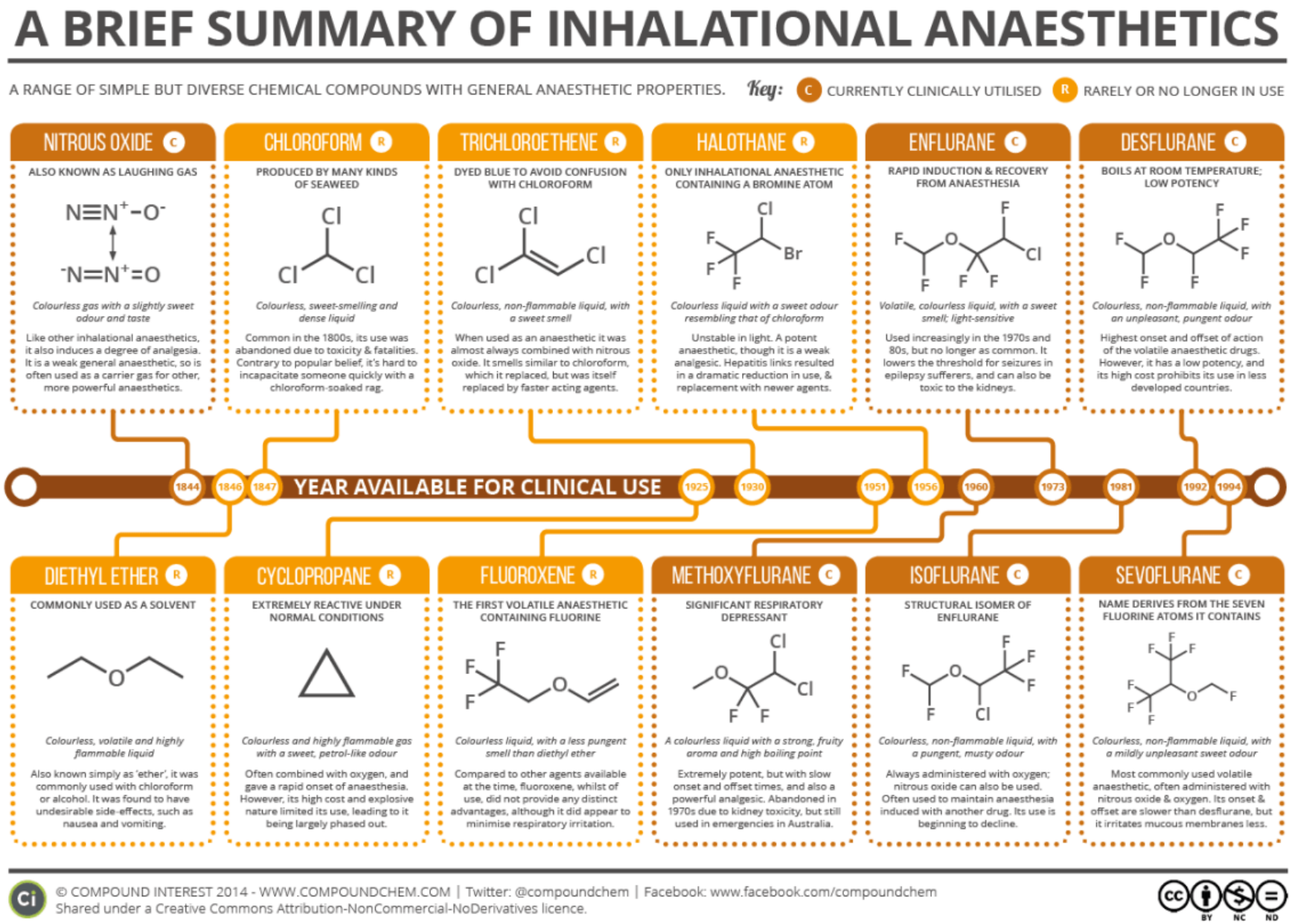
Recent data, however, have cast doubt upon this notion. Exposure of rodents to anesthetic agents during the period of birth results in widespread neurodegeneration in the developing brain. This neuronal injury, which is apoptotic in nature, results in disturbed electrophysiologic function and cognitive dysfunction in adolescent and adult rodents that were exposed to anesthetics during the neonatal period.

A variety of agents, including isoflurane, propofol, midazolam, nitrous oxide, and thiopental, manifest this toxicity.



Click to enlarge

https://i0.wp.com/www.compoundchem.com/wp-content/uploads/2014/11/Brief-Guide-to-Inhalational-Anaesthetics-2016.png?ssl=1



Click to enlarge

https://i1.wp.com/www.compoundchem.com/wp-content/uploads/2015/09/Guide-to-Intravenous-Anaesthetics.png?ssl=1