

ISOFLURANE AND HALOTHANE

MODERATOR : DR GOGNA

SPEAKER : DR SHWETA

JR 1 ANAESTHESIA

Inhalant Anesthetics

1) Volatile liquids

Ether (prototype – not used)

Halothane, Methoxyflurane (Old)

Enflurane (new)

Isoflurane (Newer)

Desflurane (Suprane) (Newest)

Sevoflurane (Ultane) (Newest)

2) Gases

N₂O (still used)

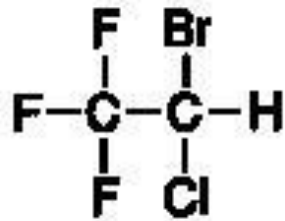
Cyclopropane (not in use)

Halogenated Organic Compounds

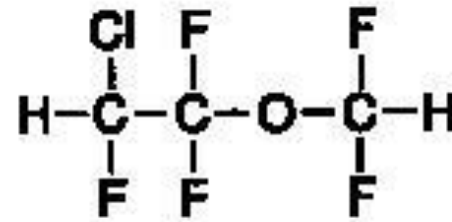
- Isoflurane and sevoflurane are the most commonly used agents in this class
- Also Desflurane, Halothane, Methoxyflurane, and Enflurane
- Liquid at room temperature
- Stored in a vaporizer on an anesthetic machine
- Vaporized in oxygen that flows through the vaporizer
 - Exception being Desflurane- has a special injection type vaporizer

Physiochemical Properties

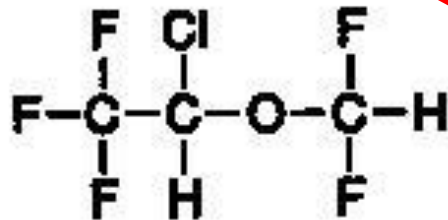
- halogenated hydrocarbons
- more dense than water
- structural isomerism
- similar molecular weights (168-220)
- 1cc produces approx 200 cc saturated vapour



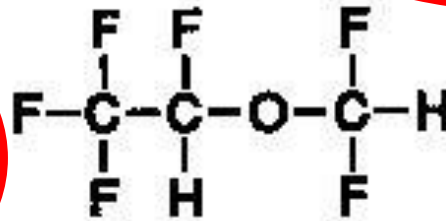
Halothane



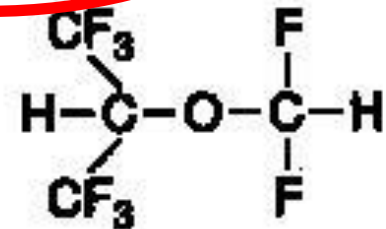
Enflurane



isoflurane



Desflurane



Sevoflurane

Vapour Pressure & BP

- © **Pressure exerted by the molecules of the vapour phase at equilibrium of molecules moving in and out of liquid phase**
- © **Vapour Pressure is dependent on temperature and physical characteristics of liquid and is independent of atmospheric pressure**
- © **↑ Temperature → ↑ Vapour Pressure**
- © ***Vapour pressure* is a measure of the agent's ability to evaporate (volatility) .The greater is the vapour pressure, the greater the concentration of inhalant deliverable to the patient (and environment).**
- © **Boiling Point: Temperature at which vapor pressure equals atmospheric pressure**

Vapour Pressure & BP

Agent	BP (°C)	VP (20 °C)
Halothane	50	243
Enflurane	56	175
Isoflurane	48	238
Sevoflurane	58	160
Desflurane	23	664
Nitrous Oxide	-89	
Xenon	-107	

Uptake and Distribution of Halogenated Organic Compounds

- Liquid anesthetic is vaporized and mixed with oxygen gas
- Mixture is delivered to the patient via a mask or endotracheal tube (ET tube)
- Mixture travels to lungs (alveoli) and diffuses into the bloodstream
- Diffusion rate is dependent on concentration gradient (alveoli/capillary) and lipid solubility
- Concentration gradient is greatest during initial induction

Uptake and Distribution of Halogenated Organic Compounds (Cont'd)

- Distribution to tissues is dependent on blood supply
 - Lipid solubility determines entry into tissues through cell walls
- Depth of anesthesia is dependent on partial pressure of anesthetic in the brain
 - Partial pressure in the brain is dependent on partial pressure of the anesthetic in blood and alveoli
- Maintenance of anesthesia is dependent on sufficient quantities of anesthetic delivered to the lungs

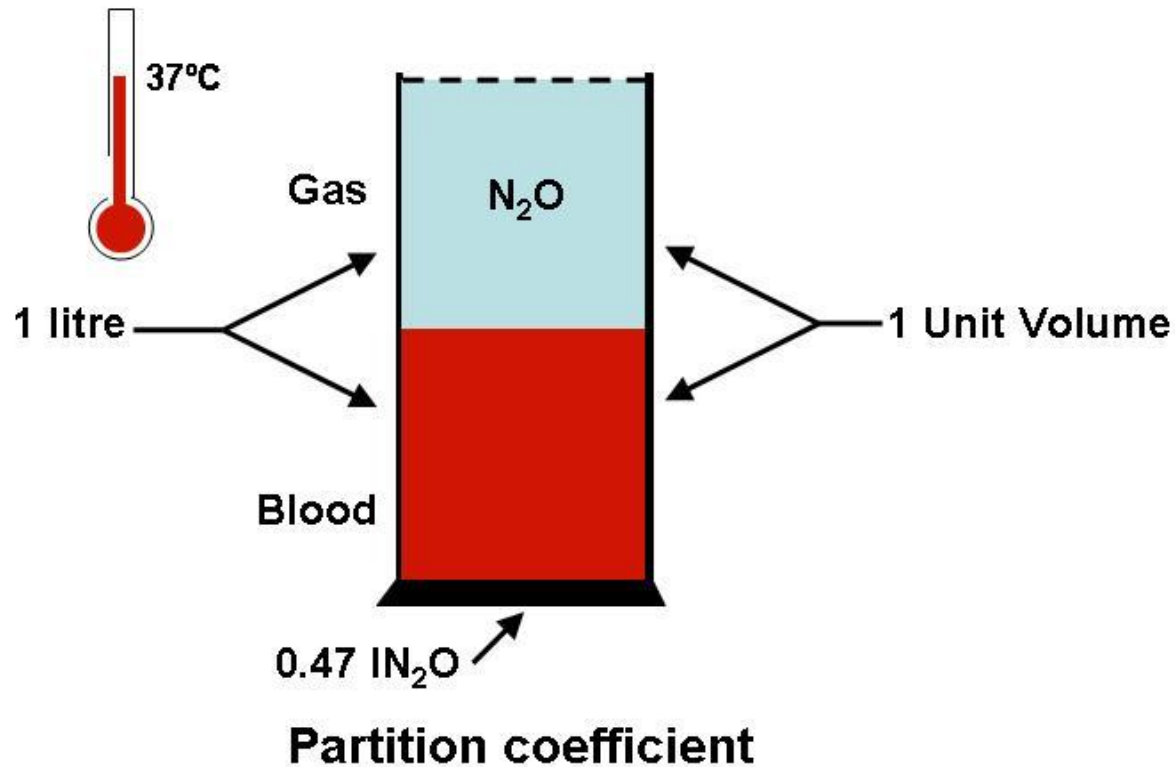
Blood : Gas Partition Coefficient

- Solubility coefficient is a ratio of concentration of an agent in 2 substances
- The measure of the solubility of an inhalation anesthetic in blood as compared to alveolar gas (air)
- Indication of the speed of induction and recovery for an inhalation anesthetic agent
- Low blood:gas partition coefficient
 - Agent is more soluble in alveolar gas than in blood at equilibrium
 - Agent is less soluble in blood
 - Faster expected induction and recovery

Blood : Gas Partition Coefficient (Cont'd)

- High blood:gas partition coefficient
 - Agent is more soluble in blood than in alveolar gas at equilibrium
 - Agent is less soluble in alveolar gas
 - Agent is absorbed into blood and tissues (sponge effect)
 - Slower expected induction and recovery

Solubility of Inhaled Drugs



Solubility of Inhaled Drugs

	Halo	Enflur	Isoflur	Sevofl	Desfl	N ₂ O
Blood/Gas	2.54	1.8	1.4	0.69	0.42	0.47
Brain/Blood	1.9	-	1.6	1.7	1.3	0.5
Fat/Blood	51	-	45	48	27	2.3

MAC

- Defined as the ***minimum alveolar concentration*** of an anesthetic agent at one atmosphere that prevents skeletal muscle movements in 50% of patients exposed to a noxious stimulus.
- Measurement of inhalation agent potency, which refers to the quantity of an agent required to produce a desired effect.
- methoxyflurane (MAC = 0.23) currently is the most potent inhalant agent available.

Margin of anaesthetic depth

	MAC skin incision	MAC awake
Halothane	0.75	0.38
Enflurane	1.63	0.5
Isoflurane	1.17	0.36
Sevoflurane	1.8	0.36
Desflurane	6.0	2.6

$(s-a)/s$

0.49

0.7

0.7

0.82

0.56

$$\frac{\text{MAC} - \text{MAC awake}}{\text{MAC}}$$

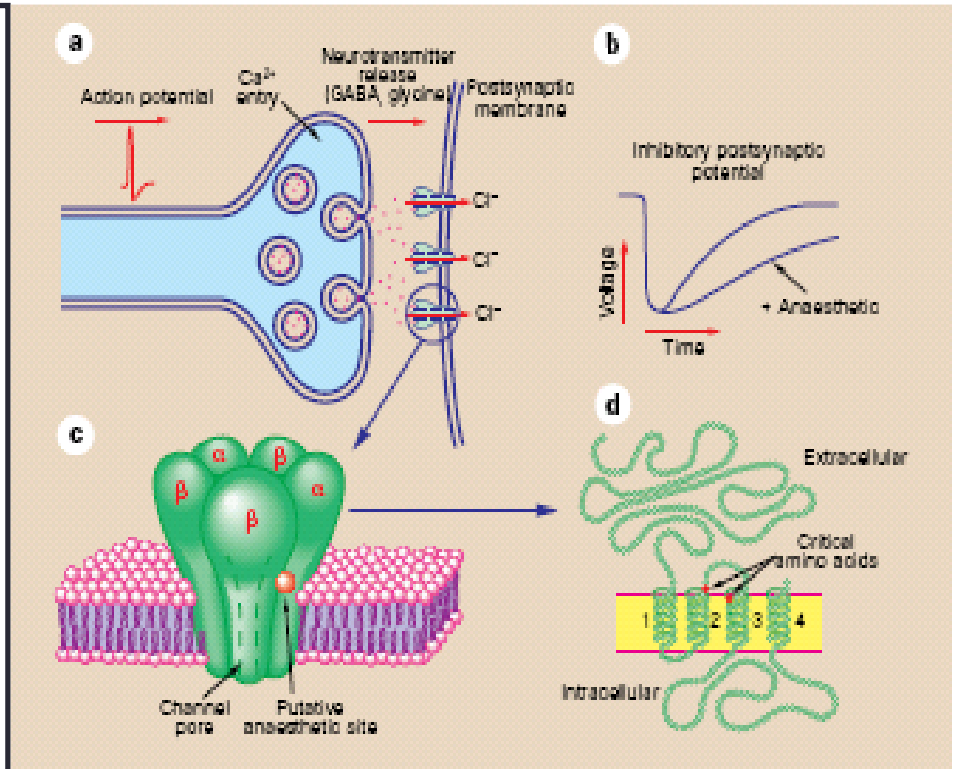
Obsolete theories of anaesthesia

Meyer Overton (potency $\propto$ lipid solubility) – BUT!

- Not all lipid soluble drugs are anaesthetics and in fact some are convulsants
- many long chain molecules do not fit the relationship

Mechanisms of Anaesthesia

- facilitation at inhibitory (chloride) GABA_A channels
- facilitation at inhibitory glycine (chloride) channels
- inhibition of excitatory NMDA (cation) channels - nitrous oxide and xenon



Halothane

Properties: nonflammable, expensive, clear, sweet non pungent odour, nonirritating, decomposes by light, **Solubility 2.3; MAC 0.75%**

Intermediate solubility in blood and high potency permits intermediate onset and recovery from anaesthesia using halothane alone or in combination

Despite its chemical stability , halothane is susceptible to decomposition to hydrochloric acid, hydrobromic acid , chloride , bromide and phosgene.

For this reason, it is stored in amber coloured bottles and often thymol is added as a preservative to prevent spontaneous oxidative decomposition

Halothane

General Information:

- Introduced in 1957
- **Rapid induction and recovery**
- Low solubility in plasma
- **Sensitizes myocardium**, good muscle relaxation
- **70% exhaled as such**, 30% metabolized in liver
- **Malignant hyperthermia** in swine reported, give **Dantrolene**, a phenytoin derivative of sk.mus.relax.
- Exposure during pregnancy cautioned.

Pharmacodynamics:

Lungs: Progressive depression, acidosis, decrease pH, given with N_2O , O_2

Heart: Myocardial depression, decreases cardiac output (CO), hypotension , **sensitizes myocardium**

Liver: **hepatitis** by repeated administration.

Isoflurane

- Most commonly used inhalant agent in North America
- Approved for use in dogs and horses; commonly used in other species



Isoflurane

General information:

- Approved in 1985 for veterinary practice
- not a convulsive agent
- malignant hyperthermia** in swine reported
- adequate muscle relaxation
- rapid** and **smooth** induction
- rapid and smooth recovery

Isoflurane

Properties: halogenated methyl ethyl ether widely used now, an isomer of enflurane, colorless, less soluble, nonflammable, stable, mild pungent odor, MAC 1.17%

Isoflurane is characterized by extreme physical stability , undergoing no detectable deterioration during 5 years of storage or on exposure to carbon dioxide absorbents or sunlight

Pharmacodynamics:

Lungs: mostly exhaled as such without any change

Heart: lesser effects, does not sensitizes the myocardium

Liver and Kidney: not injurious and can safely be administered

• Properties

- High vapor pressure: need a precision vaporizer
- Low blood:gas partition coefficient: rapid induction and recovery
- Good for induction with mask or chamber
- MAC = 1.3% to 1.63%: helps determine initial vaporizer setting
- Low rubber solubility
- Stable at room temperature; no preservatives needed = no build up in the machine

Effects and Adverse Effects

- Maintains cardiac output, heart rate, and rhythm
 - Fewest adverse cardiovascular effects
- Depresses the respiratory system
- Maintains cerebral blood flow
- Almost completely eliminated through the lungs- 0.2% metabolized by the liver
- Induces adequate to good muscle relaxation
- Provides little or no analgesia after anesthesia
- Can produce carbon monoxide when exposed to a desiccated carbon dioxide absorbent

BIOTRANSFORMATION

- Halothane is oxidized in the liver by a particular isoenzyme of CYP2E1 to its principal metabolite , trifluoroacetic acid. This metabolism can be inhibited by pretreatment with disulfiram
- Isoflurane is metabolized to trifluoroacetic acid and causes rise in serum fluoride levels without impairment of renal functions

Adverse Effects of Halogenated organic compounds

- **CNS**
 - Increased intracranial pressure in patients with head trauma or brain tumors
 - Considered safe for epileptic animals
- **Cardiovascular system**
 - Decrease blood pressure and may decrease renal blood flow
- **Respiratory system**
 - Hypoventilation
 - Carbon dioxide retention and respiratory acidosis

CNS effects of inhalational agents

- all impairs autoregulation of CBF (halothane (4x) > enflurane (2x) > isoflurane/sevoflurane/desflurane)
- effect on CBF attenuated by prior hyperventilation
- enflurane > 1.5 MAC → excitatory spikes (avoid in epileptics)
- **Neuro-protection**

Neuroprotection

- Modulation of intracellular Ca^{++} homeostasis
- Inhibition of the apoptosis initiator caspase-9
- MCA occlusion studies in rats
 - Histological & functional protection
 - Persists up to 8 weeks

Cardiovascular effects

- depression of vasomotor centre
- depression of cardiac contractility
- peripheral dilatation
- autonomic effects
- sensitization to catecholamines
- **Cardioprotection – isoflurane preconditioning phosphorylates ALDH2 and reduces ischaemic/repurfusion injury**
- Halothane sensitizes the heart to the arrhythmogenic effects of epinephrine , so that dose of epinephrine above 1.5mcg/kg should be avoided

Effects of inhalational agents on respiration

- 1 MAC isoflurane completely abolishes response to hypoxia and depresses response to hypercarbia by 50%
- enflurane most depressant and halothane least
- desflurane most irritant and sevoflurane least
- Halothane is the most bronchodilating
- Hypoxic drive is severely depressed by even low doses of halothane (0.1MAC)

General hepatic effects

- cardiac output reduced
- hepatic portal flow reduced
- increased dependence on hepatic arterial flow
- hepatic arterial bed autoregulation impaired by
halothane > enflurane > sevoflurane > isoflurane

Anaesthesia Induced Hepatitis

- Oxidative metabolism → trifluoroacetyl halide (TFA)
- TFA changes structure of CP450 & other proteins to become haptens
- dramatic immune response in susceptible individuals
- TFA antibodies common in halothane hepatitis

Anaesthesia Induced Hepatitis

- Halothane most common
- Cross-sensitivity between inhalational agents (except sevoflurane which is not metabolised to TFA)
- 70% have a history of atopy
- More common in obese middle aged women
- Patients exposed to multiple halothane anaesthetics at short intervals
- Signs are mostly related to hepatic injury , such as increased serum alanine and aspartate transferase , elevated bilirubin and encephalopathy

Halothane hepatitis: non immune-mediated

- transient, minor rise in transaminases more common than fulminant hepatitis
- may be associated with a direct hepatotoxic effect of reductive metabolites

Neuromuscular effects

- all inhalational agents potentiate the effects of neuromuscular blocking drugs
- Causes relaxation of skeletal muscles
- reduce contractility
- reduce acetylcholine release
- sevoflurane > isoflurane/desflurane > halothane

ISOFLURANE	HALOTHANE
Halogenated with flouride and chloride	Halogenated with flouride , chloride and bromide
MAC – 1.17	MAC – 0.75
Low solubility in blood and fat – faster induction and recovery from anaesthesia	Less soluble in comparison to isoflurane and slower induction and recovery
CVS – Does NOT sensitize the myocardium to the effect of circulatory cathecholamines – agent of choice in Arrhythmias (cardioprotection)	CVS – sensitizes the myocardium and therefore can lead to arrhythmias
RS – less decrease in RR and maintains TV and oxygenation	RS – hyopoxia and decrease RR and better bronchodilator
Better relaxation of skeletal muscles	Relaxes skeletal muscles to a lesser extent comparitively
CNS : neuroprotection	Depresses cerebral autoregulation
Minimal metabolism (0.2%) – low hepatic metabolism so indicated in patients with hepatic dysfunction	20% is metabolized mainly in liver and metabolites are excreted in bile and urine
Safety of isoflurane in occapational exposure – 50ppm	Occapational exposure risk is 10ppm

Thanks