Inhalation Anesthetics

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Definition :

- An inhalational anesthetic is a chemical compound possessing general anesthetic properties that can be delivered via inhalation.
- Inhalational Anesthesia refers to the **delivery of anesthetics gases or vapors to the respiratory system to produce anesthesia.**
- The main use of inhalational was to ***maintain anesthesia,*** some of them can be used as ***induction*** .

Definition :

- They are administered through a **face mask**, **laryngeal mask airway** or **tracheal tube** connected to an anesthetic vaporizer and an anesthetic delivery system.
- The famous demonstration of an **Ether** anaesthetic by **William Morton in 1846**.
- The dose of inhalational anesthetic was mentioned as MAC

Classification :

1. Gases Nitrous oxide and Xenon
2. Volatile agent

A- Fluorinated ethers (Isoflurane, Sevoflurane and Desflurane)

B- Halogenated hydrocarbon (Halothane)

Mechanisms of Action :

1* Lipid theory (Meyer–Overton relationship):

The more lipid soluble the agent (represented by a **higher** log oil/gas partition coefficient), the greater the **potency**.

Mechanisms of Action :

2* Protein site of action theory :

Throughout the CNS, there are many excitatory and inhibitory ligand-gated ion channels. There is increasing evidence that anaesthetic agents act by

a) **Inhibiting** excitatory (serotonergic, neuronal nicotinic and N-methyl-D-aspartate (**NMDA**)) channels

b) **Activating** inhibitory channels (γ-aminobutyric acid A (**GABAA**) and glycine).

Pharmacokinetic of inhalational anesthetics :

The forward movement of inhalational agent is determined by a series of partial pressure gradients, beginning at the vaporizer of the anesthetic machine, continuing in the breathing circuit, the alveolar tree, blood, and then tissue.

- The principal objective of that movement is to achieve equal partial pressures on both sides of each single barrier.

Pharmacokinetic of inhalational anesthetics :

- The alveolar partial pressure governs the partial pressure of the anesthetic in all body tissues; they all will ultimately equal the alveolar partial pressure of the gas.
- After a short period of equilibration the alveolar partial pressure of the gas equals the brain partial pressure.

So there was an uptake , ventilation and concentration that effect the induction rate and awaking time.

Pharmacokinetic of inhalational anesthetics :

- Partial pressure is the ratio of the amount of substance in one phase to the amount in another phase
- Recovery from anesthesia depends on lowering the concentration of anesthetic in brain tissue.
- Anesthetics can be eliminated by biotransformation, transcutaneous loss, or exhalation.

Pharmacokinetic of inhalational anesthetics :

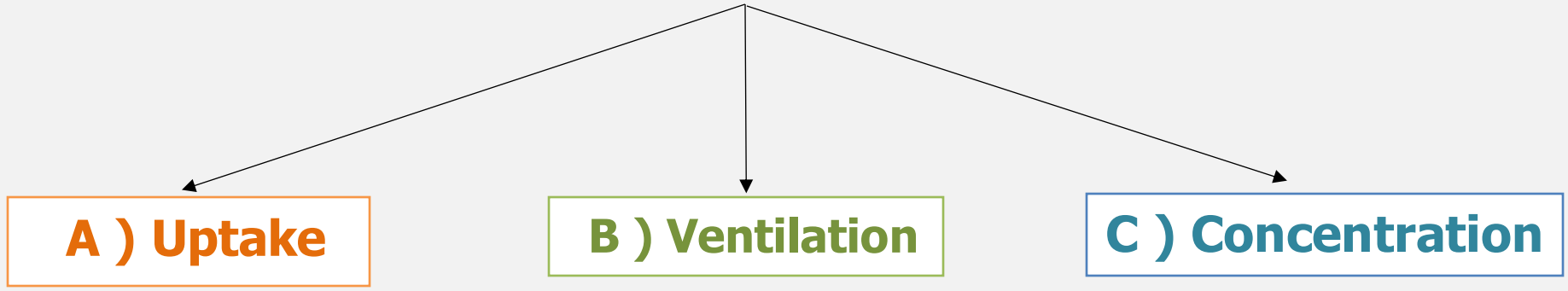
- Biotransformation usually accounts for a minimal increase in the rate of decline of alveolar partial pressure.
- Diffusion of anesthetic through the skin is insignificant.

So The most important route for elimination of inhalation anesthetics is the alveolus.

Pharmacokinetics of Inhalation Anesthetics

I) FACTORS AFFECTING INSPIRED GAS CONCENTRATION (FI)

II) FACTORS AFFECTING ALVEOLAR GAS CONCENTRATION (FA)



I) FACTORS AFFECTING INSPIRED GAS CONCENTRATION (FI)

1. Fresh Gas Flow Rate ↗ (Increase)
2. Volume of Breathing system ↘ (Decrease)
3. Gas Absorption by anaesthetic machine or breathing circuit ↘ (Decrease)

So Inspired Gas Concentration near to fresh gas Concentration

II) FACTORS AFFECTING ALVEOLAR GAS CONCENTRATION (FA) :

A) Uptake :

Uptake $\frac{1}{\propto}$ alveolar gas Concentration

- If Decrease or no uptake (alveolar gas Concentration reach to the inspired gas Concentration)
- If uptake ↗ → slow raise in alveolar Concentration slow induction

What is MAC ? :

Minimum Alveolar Concentration :

- Minimal alveolar concentration of inhalational agent that prevent movement in 50% of the patients in response to surgical stimulation (skin incision)
- Equivalent to ED50
- For the same agent, varies with age, temperature and other drugs on board

Ideal Characteristics of inhalational anesthetics:

1. Non-flammable, non-explosive at room temperature.
2. Stable in light.
3. Liquid and vaporizable at room temperature.
4. Stable at room temperature, with a long shelf life.
5. Stable with soda lime, as well as plastics and metals.

Ideal Characteristics of inhalational anesthetics:

7. Environmentally friendly - no ozone depletion.
8. Cheap and easy to manufacture.
9. Non toxic.
10. Rapid induction and rapid recovery.
11. Safe with no toxic side effect.

Common Undesirable effects of the volatile agents :

1. They all depress respiration.
2. Reduce uterine tone .
3. Trigger MH (Malignant Hyperthermia) .
4. All increase cerebral blood flow and ICP.

MAC is reduced by :

- Nitrous oxide.
- Hypothyroid/myxedema.
- Hypocapnia.
- Hypothermia-decrease is roughly linear.
- Hyponatraemia.
- Increasing age.

MAC is reduced by :

- Hypoxaemia.
- Hypotension.
- Anemia.
- Pregnancy.
- CNS depressant drugs.
- Other drugs: lithium, lidocaine, magnesium, Acute alcohol abuse .

MAC is increased by :

- Hyperthermia.
- Hypernatraemia.
- Sympatho-adrenal stimulation.
- Chronic alcohol abuse.

MAC is increased by :

- Chronic opioid abuse.
- Increases in ambient pressure.
- Hypercapnia.
- Decreasing age.
- Thyrotoxicosis .

MAC (HINT) :

Sex, Weight and Duration of anesthesia does not affect MAC

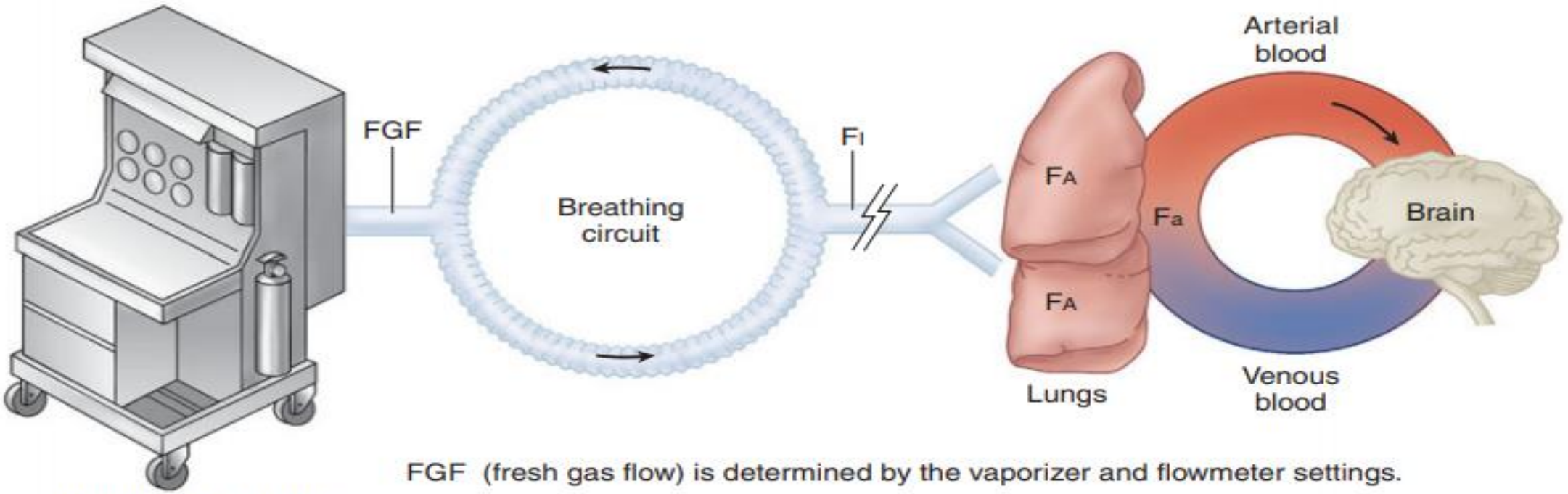
Nitrous oxide MAC105%

Halothane (Fluothane) 0.75%

Isoflurane 1.2%

Desflurane 6.0%

Sevoflurane 2.0 %



FGF (fresh gas flow) is determined by the vaporizer and flowmeter settings.

FI (inspired gas concentration) is determined by (1) FGF rate; (2) breathing-circuit volume; and (3) circuit absorption.

FA (aveolar gas concentration) is determined by (1) uptake (uptake = λb/g x C(A-V) x Q); (2) ventilation; and (3) the concentration effect and second gas effect:
- a) concentrating effect
- b) augmented inflow effect

Fa (arterial gas concentration) is affected by ventilation/perfusion mismatching.

FIGURE 8–1 Inhalation anesthetic agents must pass through many barriers between the anesthesia machine and the brain.

Inhalation Anesthetics :

TABLE 8–2 Tissue groups based on perfusion and solubilities.

Characteristic	Vessel Rich	Muscle	Fat	Vessel Poor
Percentage of body weight	10	50	20	20
Percentage of cardiac output	75	19	6	0
Perfusion (mL/min/100 g)	75	3	3	0
Relative solubility	1	1	20	0

Nitrous Oxide : Physical proprieties :

- It is inorganic anesthetic gas
- Slightly sweet-smelling gas
- Non-flammable but supports combustion
- Breaking down to O2 and nitrogen at high temperatures.
- Supplied as a **liquid/gas** in French blue cylinders

Nitrous Oxide : Physical proprieties :

- Ice often forms on the cylinder during use
- It is colorless and essentially odorless
- It is stored as a **liquid** in **blue** cylinders with a gauge pressure of 51bar at 20ºC.
- The gauge pressure does not give an indication of cylinder content until all the remaining N2O is in the gaseous phase.
- It is more diffusible than oxygen or nitrogen

Nitrous Oxide : Induction and recovery:

- Fast onset and recovery;
- strongly analgesic but weakly anaesthetic.
- It is widely used in obstetric practice to relieve pain during childbirth and in minor surgical procedures.
- Useful analgesic for dental extraction
- Both induction and recovery from anaesthesia are extremely rapid.

Nitrous Oxide : Induction and recovery:

- It's previously known as (**laughing gas**)
- It rapidly enters enclosed air-containing spaces more rapidly than oxygen or
  nitrogen can leave. These spaces include the **cuff** of an endotracheal tube, the **bowel**, **pneumothorax** ,the **middle ear**, **nasal sinuses** and the eye and air **emboli**, and nitrous oxide will increase their volume .
- It may cause postoperative temporary hypoxia (**diffusion hypoxia**).

Nitrous Oxide : Side Effects :

Respiratory :

- Non-irritant. Depresses respiration slightly.
- May cause diffusion hypoxia at the end of surgery.

Cardiovascular :

- Mild direct myocardial depression which is offset by an increase in sympathetic activity via its central effects.(Little effect on heart rate and BP usually)

Central nervous system :

- Increases cerebral metabolism, cerebral blood flow and ICP slightly.

Toxicity :

- It interferes with DNA synthesis even after relatively brief exposure.

Nitrous Oxide : Others :

- Post operative nausea and vomiting
- Does not affect hepatic or renal function, nor uterine or skeletal muscle tone.
- Prolonged use may cause bone marrow depression, megaloblastic anaemia and peripheral neuropathy.
- Generally considered as being safe during pregnancy

Xenon :

- It Is a noble gas with an anaesthetic effect.
- Xenon is a nearly ideal anaesthetic agent.
- At a concentration of 70% mixed with 30% oxygen it induces general anaesthesia without side effects.
- It cannot be synthetized and is isolated from air, which contains 0.0000087% xenon.
- inert and odourless gas.

Xenon :

* very fast onset and offset of anaesthesia (low blood:gas partition coefficient)
* Expensive
* It is not metabolized and is excreted unchanged via the lungs.
* It is non-toxic, not flammable,
* non-irritant to the airway.
* Xenon has analgesic properties
* Muscle relaxation at higher concentrations.

Xenon :

- Minimal cardiovascular effects
- (small decrease in heart rate only)
- Minimal respiratory effects (slows respiratory rate slightly, but increase tidal volume to compensate).
- It does not cause malignant hyperthermia.

Halothan :

- Halothane is a highly soluble agent with a **high** blood–gas partition coefficient and its **MAC** is (0.75)

Halothan : Physical Properties

- It corrodes certain metals and dissolves into rubber.
- Its use rapidly spread because of its greater potency, ease of use, non-irritability and non-inflammability .
- Risks of arrhythmias and liver damage on repeated administration (halothane hepatitis) .
- Halothane is the least expensive volatile anesthetic.

Halothan : Effects

Respiratory :

- Depress Minute ventilation largely due to decreased tidal volume
- The normal response to hypoxia and hypercarbia are blunted.
- It has a sweet non-irritant odour and may be used for gaseous induction.
- Halothane also bronchodilator and is useful in asthmatic patients.
- Non-irritant. Pharyngeal, laryngeal and cough reflexes are abolished early
- Respiratory depressant, with increased respiratory rate and reduced tidal volume.
- Inhibition of secretions .

Halothan : Effects

- ***Cardiovascular :***
- Myocardial depression and bradycardia.
- Hypotension is common. (reduce sys. Vascular resistance)
- Myocardial O2 demand decreases.
- Arrhythmias are common, e.g. Bradycardia, ectopic.
- Sensitizes the myocardium to catecholamines, e.g. Endogenous or injected adrenaline.

Halothan : Effects

- ***Central nervous system :***
- Smooth rapid induction, with rapid recovery.
- Anticonvulsant action.
- Increases cerebral blood flow but reduces intraocular pressure.

Halothan : Others Effects

- Dose-dependent uterine relaxation.
- Nausea/vomiting is uncommon.
- May precipitate Malignant Hyperthermia.
- Up to 20% is metabolized in the liver.
- Repeat administration after recent use may result in hepatitis.

Halothan : Toxicity

- Hepatic damage (halothane hepatitis)
- Factors include: multiple exposures, obesity, middle age and female sex.
- Mortality is around 50-75%.
- Halothane should be avoided:

  1- If it has been given in the previous 3 months

  2- If there is a past history of adverse reaction to halothane

  3- If there is preexisting liver disease.

Halothan : Contraindications

- Severe hypovolemia
- Malignant hyperthermia
- Intracranial hypertension
- Halothane hepatitis

Isoflurane : Physical proprieties:

- Colorless liquid
- Pungent odor
- MAC 1.20
- Non-flammable, non-corrosive.
- With no additive.
- Relatively insoluble and has a blood– gas partition coefficient. **low**
- Is **widely used for** maintenance of anaesthesia and treatment of severe asthma in patients requiring mechanical ventilation in ICU.

Isoflurane : Effects :

Central nervous system :

- Smooth, rapid induction, but speed of uptake is limited by respiratory irritation.
- Recovery is slower than with sevoflurane and desflurane.
- Anticonvulsant properties
- Reduces Cerebral Metabolic Rate of O2.
- Increases cerebral blood flow and ICP.
- Decreases intraocular pressure.
- Has poor analgesic properties.

Isoflurane : Effects :

Respiratory :

- Irritant; more likely to cause coughing and laryngospasm(gaseous induction is **not** recommended)
- Respiratory depressant(more than halothane), with increased rate and decreased tidal volume.
- Causes bronchodilation.

Isoflurane : Other Effects :

- Dose-dependent uterine relaxation.
- Nausea/vomiting is uncommon.
- Skeletal muscle relaxation
- May precipitate MH.
- Widely used in neurosurgery

Isoflurane : Contraindications:

- Severe hypovolemia
- Malignant hyperthermia
- Intracranial hypertension

SEVOFLURANE :

It was originally used as an inhalational agent in Japan and is now widely used in the world, particularly in paediatric practice. Sevoflurane is relatively **insoluble** in blood and has a low blood–gas partition coefficient.

SEVOFLURANE : Physical proprieties:

- Colorless liquid
- Pleasant smelling
- MAC is (2)
- Non-flammable, non-corrosive, stable at ambient temperatures
- Supplied in liquid form with no additive.
- Interacts with soda lime to produce compounds A
- Non-pungent, low solubility- excellent for inhalation induction
- muscle relaxation (enough for pediatrics intubation)
- potentiates NMBA. (Neuromuscular Blocking Agents)
- The degradation of sevoflurane by soda lime and baralyme is results in the formation of Compound A which may cause renal tubular necrosis

SEVOFLURANE : Effects:

Respiratory

- Well-tolerated
- Minimal airway irritation.
- Respiratory depressant, with increased rate and decreased tidal volume.
- Causes bronchodilatation.

SEVOFLURANE : Effects:

Cardiovascular :

- Heart rate and contractility are unchanged, but a fall in SVR leads to a reduction in blood pressure.
- Vasodilatation and hypotension may occur
- Myocardial O2 demand decreases.
- Arrhythmias uncommon .

SEVOFLURANE : Effects:

Central nervous system :

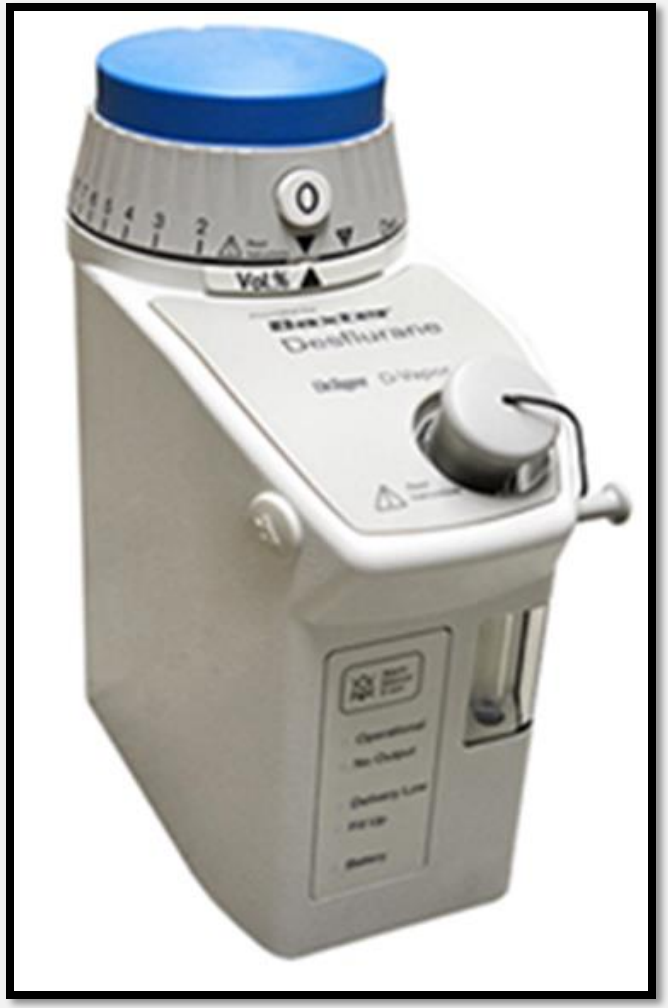
- Smooth, extremely rapid induction and recovery.
- Early postoperative analgesia may be required as emergence
- Is so rapid.
- Increases the risk of emergence agitation
- Anticonvulsant properties.
- Reduces cerebral metabolic rate of O2
- Decreases intraocular pressure.
- Has poor analgesic properties

SEVOFLURANE : Others Effects:

- Dose-dependent uterine relaxation.
- Nausea/vomiting occurs.
- Skeletal muscle relaxation
- May precipitate MH.
- Tracheal intubation may be performed easily with spontaneous Respiration.
- Considered the agent of choice for inhalational induction in pediatrics because of its rapid and smooth induction characteristics.
- Has also been used for the difficult airway, including airway obstruction.

DESFLURANE :

- Its low blood: gas partition coefficient results in fast onset and offset of action. These properties make it ideal for long procedures where rapid wake-up is important to assess the patient.



DESFLURANE : Physical proprieties:

Introduced in the UK in 1994

a colorless liquid with slightly pungent vapor

boiling point: 23°C, MAC: 5%–7% in adults; 7.2%–10.7% in children

non-flammable, non-corrosive

supplied in liquid form with no additive

may react with dry soda lime to produce carbon monoxide

Desflurane uses specific electrically powered vaporizer (Tec 6) due to its low boiling point.

DESFLURANE : Effects:

Respiratory :

1) Causes airway irritation; not recommended for induction of anesthesia because respiratory complications (e.g. laryngospasm, breath-holding, cough, apnea) are common and may be severe.

2) Respiratory depressant, with increased rate and decreased tidal volume.

DESFLURANE : Effects:

Cardiovascular :

1) Vasodilatation and hypotension may occur, similar to isoflurane, may cause tachycardia and hypertension via sympathetic stimulation, especially if high concentrations are introduced rapidly.

2) Myocardial ischemia may occur if sympathetic stimulation is excessive, but has cardioprotective effects in patients undergoing cardiac surgery.

3) Arrhythmia as uncommon, as for isoflurane, little myocardial sensitization to catecholamines.

4) Renal and hepatic blood flow generally preserved.

DESFLURANE : Effects:

Central nervous system

1) Rapid induction (although limited by its irritant properties) and recovery.

2) May increase cerebral blood flow, although the response of cerebral vessels to CO2 is preserved.

3) ICP may increase due to imbalance between the production and absorption of CSF.

4) Reduces CMRO2 as for isoflurane.

5) Has poor analgesic properties.

DESFLURANE : Others Effects:

- 0.02% of Desflurane undergoes metabolism by liver
- Dose-dependent uterine relaxation (although less than isoflurane and sevoflurane).
- Skeletal muscle relaxation; non-depolarising neuromuscular blockade may be potentiated

DESFLURANE : Contraindications :

- Severe hypovolemia
- Malignant hyperthermia
- Intracranial hypertension

Advantages and disadvantages of the modern volatile anaesthetic agents

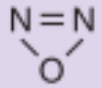
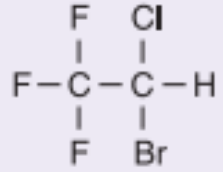
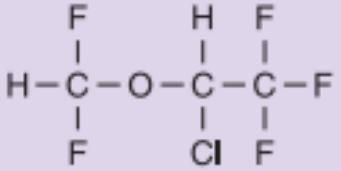
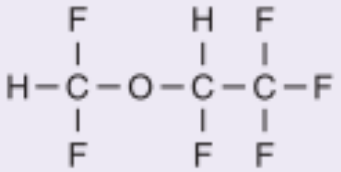
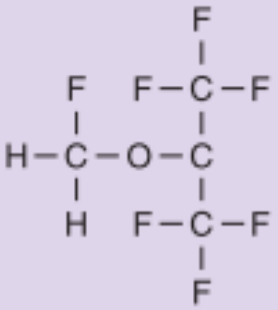
	Isoflurane	Sevoflurane	Desflurane
Advantages	• Low cost; approximately 70% cheaper than sevoflurane • Bronchodilator • No significant toxic metabolites • Non-arrhythmogenic	• Good for inhalational induction • Non-irritant to airways • Faster onset/offset than isoflurane • Non-arrhythmogenic	• Fast onset/recovery from anaesthesia • Minimal, non-toxic metabolites
Disadvantages	• Concerns about coronary steal syndrome • Irritant to airways	• Expensive • Metabolised to toxic metabolites (not thought to be of clinical concern) • Formation of potentially toxic compounds on interaction with soda lime/ baralyme (not thought to be of clinical concern)	• Expensive • Irritant to airways • Causes tachycardia at higher concentrations • Heated/pressurised vaporiser required for delivery

All volatile agents:

- may trigger malignant hyperpyrexia in susceptible individuals;
- have a higher incidence of PONV compared with total intravenous anaesthesia; PONV : Post Operative Nausea Vomiting
- have a possible association with postoperative cognitive dysfunction
- are environmental greenhouse gases; and
- cause dose-dependent CVS/RS depression.

Table 6 :

TABLE 8–3 Properties of modern inhalation anesthetics.

Agent	Structure	MAC%[1]	Vapor Pressure (mm Hg at 20°C)
Nitrous oxide		105[2]	—
Halothane (Fluothane)		0.75	243
Isoflurane (Forane)		1.2	240
Desflurane (Suprane)		6.0	681
Sevoflurane (Ultane)		2.0	160

[1]These minimum alveolar concentration (MAC) values are for 30- to 55-year old human subjects and are expressed as a percentage of 1 atmosphere. High altitude requires a higher inspired concentration of anesthetic to achieve the same partial pressure.

[2]A concentration greater than 100% means that hyperbaric conditions are required to achieve 1.0 MAC.

TABLE 8–6 Clinical pharmacology of inhalational anesthetics.

	Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular					
Blood pressure	N/C[1]	↓↓	↓↓	↓↓	↓
Heart rate	N/C	↓	↑	N/C or ↑	N/C
Systemic vascular resistance	N/C	N/C	↓↓	↓↓	↓
Cardiac output[2]	N/C	↓	N/C	N/C or ↓	↓
Respiratory					
Tidal volume	↓	↓↓	↓↓	↓	↓
Respiratory rate	↑	↑↑	↑	↑	↑
$Paco_2$					
Resting	N/C	↑	↑	↑↑	↑
Challenge	↑	↑	↑	↑↑	↑
Cerebral					
Blood flow	↑	↑↑	↑	↑	↑
Intracranial pressure	↑	↑↑	↑	↑	↑
Cerebral metabolic rate	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Neuromuscular					
Nondepolarizing blockade[3]	↑	↑↑	↑↑↑	↑↑↑	↑↑
Renal					
Renal blood flow	↓↓	↓↓	↓↓	↓	↓
Glomerular filtration rate	↓↓	↓↓	↓↓	↓	↓
Urinary output	↓↓	↓↓	↓↓	↓	↓
Hepatic					
Blood flow	↓	↓↓	↓	↓	↓
Metabolism[4]	0.004%	15% to 20%	0.2%	<0.1%	5%

[1]N/C, no change.
[2]Controlled ventilation.
[3]Depolarizing blockage is probably also prolonged by these agents, but this is usually not clinically significant.
[4]Percentage of absorbed anesthetic undergoing metabolism.