

Pharmacology of Inhalational Anaesthetics

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Summary

Inhalational anaesthetics produce loss of consciousness, but may have other effects including analgesia (nitrous oxide) or muscle relaxation (isoflurane). They are presented as liquefied gases under pressure or as volatile liquids.

MODE OF ACTION

The molecular basis of inhalational anaesthesia is not fully understood. Historically, the first observation that had a significant impact was the Meyer-Overton hypothesis which demonstrated that the potency (expressed as minimum alveolar concentration, MAC - see below) of an anaesthetic agent increased in direct proportion to its oil:gas partition coefficient (see Figure 1). This led to the interpretation that the site of action of general anaesthetics was the lipid bilayer of nerve membranes and that when a sufficient amount of drug was dissolved in this layer, then anaesthesia occurred. There were several theories as to the molecular mechanism, but each with its own limitations.

More recent research suggests that inhalational agents may act on specific membrane proteins and alter ion flux or receptor function. This is supported by the fact that anaesthetic enantiomers (optical isomers) usually display different anaesthetic potencies in animals. The prime candidates for protein targets are:

GABA_A receptors - potentiation of GABA at this receptor occurs with halothane, isoflurane and sevoflurane.

Glycine receptors - these are often at the same CNS sites as the GABA_A receptors and are of particular

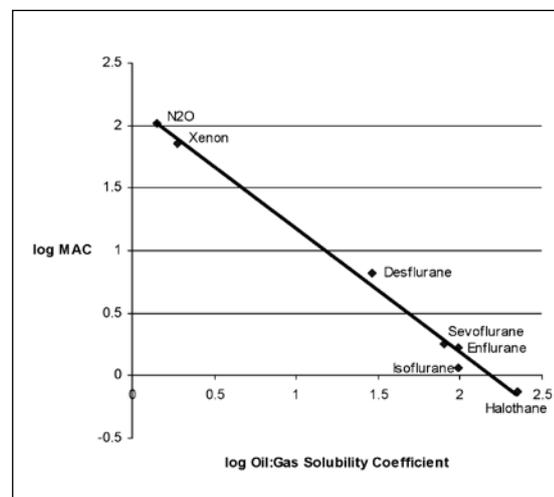


Figure 1. Relationship between MAC and oil:gas solubility coefficient

importance in lower brain centres and the spinal cord. Potentiation of glycine receptors is seen at low concentrations for all the volatile agents.

Two-pore-domain potassium channels - these have subunits that are activated by volatile and gaseous anaesthetics and may modulate membrane excitability and have a complex distribution within the CNS. Other possible targets may include NMDA receptors, HCN channels and some subtypes of the sodium channel.

POTENCY

The potency of an inhalational anaesthetic agent can be measured by its MAC. This is defined as the minimum alveolar concentration at steady-state that prevents reaction to a standard surgical stimulus (skin incision) in 50% of subjects at 1 atmosphere. MAC is affected by a wide range of physiological and pharmacological factors (see Table 1) and is additive when a mixture of agents are used together.

PHARMACOKINETICS

When inhaled agents have reached steady-state, the partial pressure within the alveoli (P_A) is in equilibrium with that in the arterial blood (P_A) and the brain (P_B). In this way, P_A gives an indirect measure of P_B . However, this steady-state is rarely achieved in the clinical setting as the process may take many hours, depending upon the agent and a range of physiological factors as below.

Ventilation

Increased alveolar ventilation results in a faster rise in P_A and therefore P_B will also rise more quickly, reducing the onset of anaesthesia time. Functional residual capacity (FRC) is also significant. A large functional residual capacity (FRC) will effectively dilute the inspired concentration and increase the onset time whereas a small FRC will allow P_A to rise rapidly.

Inspired concentration of inhalational agent

Increasing the inspired concentration of inhaled anaesthetic agent leads to a more rapid rise in P_A and so reduces onset time.

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Table 1. Factors affecting the MAC of an inhalational agent

	Effect on MAC
Physiological and metabolic factors	
Age	
Infancy and childhood	↑
Neonatal period and old age	↓
Pregnancy	↓
Hyperthermia	↑
Hypothermia	↓↓
Hyperthyroidism	↑
Hypothyroidism	↓
Hypernatraemia	↑
Pharmacological factors	
Catecholamines and sympathomimetics	↑
α ₂ agonists	↓
Sedatives	↓↓
Opioid analgesics	
acute use	↓
chronic use	↑
Alcohol	
acute intake	↓
chronic intake	↑
Amphetamines	
acute dosage	↑↑↑
chronic dosage	↓
Lithium	↓

Cardiac output

Changes in cardiac output affect pulmonary capillary transit time. During the induction of anaesthesia, a low cardiac output reduces anaesthetic uptake, but it actually accelerates the rise in PA and therefore the onset of anaesthesia. This effect is only important when agents with a high blood:gas partition coefficient are used (see below).

Blood:gas partition coefficient

The blood:gas partition coefficient is defined as the ratio of the amount of anaesthetic in blood and gas when the two phases are of equal

volume and pressure and in equilibrium at 37°C. Intuitively it would be expected that agents with a high blood:gas partition coefficient (and therefore high solubility) would have a rapid onset. However, this is not the case as these agents will only exert a low partial pressure in blood, even when present in large amounts. The crucial factor determining onset of anaesthesia is the partial pressure of the agent in the blood (PA) and subsequently in the brain (PB). Therefore agents with a low blood:gas partition coefficient will exert a high partial pressure and produce a more rapid onset and offset of action.

Metabolism

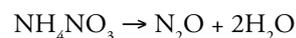
Halogen ions are released following metabolism by hepatic cytochrome p450 enzymes and have the potential to cause hepatic or renal damage. The C-F bond is relatively stable and only minimally metabolized, whereas C-Cl, C-Br and C-I bonds become progressively easier to metabolise (see Table 2).

PROPERTIES OF INDIVIDUAL INHALATIONAL ANAESTHETIC AGENTS

In this section, we will look at each agent in more detail and compare their properties. The chemical structures of the agents are diverse, and include an elemental gas (Xenon), an inorganic gas (nitrous oxide), a halogenated hydrocarbon (halothane), halogenated ethyl methyl ethers (isoflurane, enflurane, desflurane) and a polyfluorinated isopropyl methyl ether (sevoflurane) - see Figure 2. Isoflurane and enflurane are structural isomers of each other. Unlike the other volatile agents, sevoflurane is achiral. Their physiochemical properties are also diverse and are summarised in Table 3. The pharmacodynamic effects are summarised in Table 4 at the end of this section.

NITROUS OXIDE (N₂O)

N₂O has a high MAC and is widely use in combination with other inhaled anaesthetic agents or with O₂ as entonox. However, it interferes with DNA synthesis even after relatively brief exposure. It is manufactured by heating ammonium nitrate to 250°C, and impurities are removed by passage through scrubbers, water and caustic soda:



N₂O is stored as a liquid in French blue cylinders with a gauge pressure of 51bar at 20°C. The gauge pressure does not give an indication of cylinder content until all the remaining N₂O is in the gaseous phase. The filling ratio of the cylinders (defined as the mass of N₂O in the

Table 2. Metabolism of inhaled anaesthetic agents

Agent	Percentage Metabolized	Metabolites
N ₂ O	<0.01	(N ₂)
Halothane	20	Trifluoroacetic acid, Cl, Br
Sevoflurane	3.5	Inorganic & organic fluorides Compound A in the presence of soda lime and heat (Compounds B, C, D & E)
Enflurane	2	Inorganic & organic fluorides
Isoflurane	0.2	Trifluoroacetic acid and F ⁻
Desflurane	0.02	Trifluoroacetic acid

Table 3. *Physicochemical properties of inhaled anaesthetics*

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane	N₂O	Xenon
MW	197.0	184.5	184.5	168.0	200.1	44.0	131.0
BP (°C)	50.2	48.5	56.5	23.5	58.5	-88.0	-108
SVP at 20°C (kPa)	32.3	33.2	23.3	89.2	22.7	5200	
MAC (%)	0.75	1.17	1.68	6.60	1.80	105	71.0
Blood:gas partition coefficient	2.40	1.40	1.80	0.45	0.70	0.47	0.14
Oil:gas partition coefficient	224	98	98	29	80	1.4	1.9
Odour	Non-irritant, sweet	Irritant	Non-irritant	Pungent	Non-irritant	Odourless	Odourless

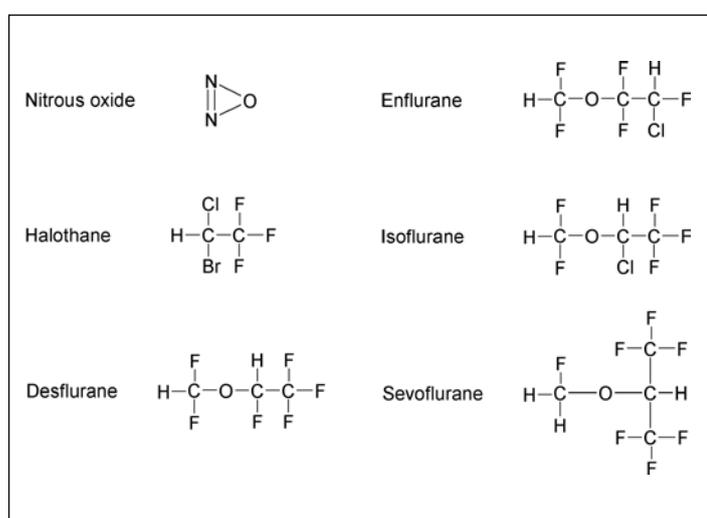


Figure 2. *Chemical structure of inhaled anaesthetics agents*

cylinder divided by the mass of water that the cylinder could hold) is 0.75 in temperate regions, but reduced to 0.67 in tropical areas to avoid cylinder explosions. It has a critical temperature of 36.5°C and its critical pressure is 72 bar (see page 131 - 'Gases and vapours').

Effects

Respiratory

- Small fall in tidal volume that is offset by an increased respiratory rate.

Cardiovascular

- Mild direct myocardial depression which is offset by an increase in sympathetic activity via its central effects.
- However, in patients with cardiac failure there may be a significant reduction in cardiac output.

Central nervous system

- Cerebral blood flow (CBF) is increased.

Concentration effect, second gas effect and diffusion hypoxia

Despite the low blood:gas solubility coefficient of N₂O, it is about 20 times more soluble than O₂ and N₂. During induction with high

concentrations of N₂O, the volume of N₂O entering the pulmonary capillaries will be significantly greater than the volume of N₂ entering the alveolus. As a consequence, the volume of the alveolus decreases, thereby increasing fractional concentrations of the remaining gases.

The concentration effect refers to the disproportionate rise in alveolar partial pressure and its high rate of approximation to the inhaled concentration. It is only seen with N₂O as it is the only agent to be present in high enough concentration and occurs due to two processes. First, the concentrating effect of the rapid N₂O uptake (as described above) and second, increased ventilation as dead space gas is drawn in to the alveolus to make up for the diminished volume.

The second gas effect is a result of the concentration effect. Volatile agents given in combination with high concentrations of N₂O will be concentrated resulting in a higher alveolar partial pressure and reduced induction time.

Diffusion hypoxia is due to the reverse of the concentration effect. At the end of anaesthesia when N₂O/O₂ is replaced with N₂/O₂, the volume of N₂O entering the alveolus from blood will be greater than the volume of N₂ entering the pulmonary capillaries resulting in dilution of all the alveolar gases including O₂. If supplemental O₂ is not given at this point, then diffusion hypoxia could result.

As well as these effects seen across the alveolar membrane, N₂O will cause a rapid expansion of any air filled spaces such as pneumothorax, vascular air embolus and luminal bowel gas.

Toxicity

N₂O oxidises the cobalt ion in vitamin B₁₂, which prevents its action as the cofactor for methionine synthase. Methionine synthase also appears to be inhibited directly by N₂O. The result is reduced synthesis of methionine, thymidine, tetrahydrofolate and DNA. Exposure of only a few hours may result in megaloblastic changes in bone marrow, and prolonged exposure may result in agranulocytosis and neurological syndromes that resemble subacute combined degeneration of the cord due to chronic vitamin B₁₂ inactivation. Teratogenicity has been shown in rats, but not convincingly demonstrated in humans, although N₂O is often avoided in the first trimester.

HALOTHANE

Halothane is unstable when exposed to light, corrodes certain metals

and dissolves into rubber. It is presented with 0.01% thymol to prevent liberation of free bromine.

Effects

Respiratory

- Minute ventilation is depressed largely due to decreased tidal volume and 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 bronchodilates and is useful in asthmatic patients.

Cardiovascular

- Bradycardia is produced by increased vagal tone, depressed sino atrial and atrio-ventricular activity.
- It also directly depresses the myocardium and systemic vascular resistance (SVR) is reduced.
- Halothane sensitizes the heart to catecholamines which may lead to arrhythmias and the quantity of adrenaline used for infiltration should be limited.

Central nervous system

- Cerebral blood flow is increased more than any other volatile agent leading to significant increases in intra-cranial pressure (ICP). However, cerebral oxygen requirements are reduced.

Metabolism

- As much as 25% of halothane undergoes oxidative metabolism by hepatic cytochrome p450 to produce trifluoroacetic acid, Br⁻ and Cl⁻. However, when the liver becomes hypoxic, reductive metabolism predominates, producing F⁻.

Toxicity

- Hepatic damage can take one of two forms:
- Reversible form - often subclinical and is associated with a rise in hepatic transaminases. This is probably due to hepatic hypoxia.
- Fulminant hepatic necrosis ('halothane hepatitis') - trifluoroacetyl chloride may behave as a hapten which binds to hepatic proteins and induces antibody formation. Diagnosis is by exclusion, and risk factors include: multiple exposures, obesity, middle age and female sex. Mortality is around 50-75%. The incidence in adults is 1 in 2500-35000.
- Halothane should be avoided if it has been given in the previous 3 months, if there is a past history of adverse reaction to halothane, or if there is pre-existing liver disease.

ISOFLURANE

Isoflurane is widely used for maintenance of anaesthesia.

Effects

Respiratory

- Ventilation is depressed more than halothane, but less than enflurane.
- Minute ventilation is decreased, respiratory rate and PaCO₂ are increased.

- It has a pungent smell and can cause upper airway irritability and breath-holding so gaseous induction is not recommended. However it does cause some bronchodilation.

Cardiovascular

- The main effect is to reduce SVR resulting in compensatory tachycardia and only a small decrease in myocardial contractility.
- It has been proposed that isoflurane may cause 'coronary steal' whereby normally responsive coronary arterioles are dilated and divert blood away from areas supplied by diseased and unresponsive vessels, resulting in ischaemia. However, recent work suggests that if coronary perfusion is maintained, coronary steal does not occur.
- Isoflurane may also have myocardial protective properties via its effects on ATP-dependent potassium channels.

Central nervous system

- Of all the volatile agents, isoflurane produces the best balance of reduced cerebral oxygen requirement and minimal increase in CBF.

Toxicity

- Carbon monoxide may be produced by a reaction between the -CHF₂ group and dry soda lime (or baralyme). Enflurane and desflurane may also react in a similar manner.

ENFLURANE

Its use has decreased due to newer agents with more favourable profiles.

Effects

Respiratory

- Causes more depression of ventilation than the other agents with a reduction in minute volume and increase in PaCO₂. The response to hypercarbia is blunted.

Cardiovascular

- Heart rate increases, but cardiac output, contractility, systemic vascular resistance and blood pressure fall.

Central nervous system

- High concentrations of enflurane in the presence of hypocarbia produce a 3Hz spike and wave pattern on the EEG consistent with grand mal activity. It is therefore usually avoided in epileptic patients.
- There is an increase in CBF and ICP to a degree in-between halothane and isoflurane.

Metabolism

- Only 2% is metabolized by hepatic cytochrome P450. F⁻ ions are produced, but rarely reach the concentration (> 40 mcml.l⁻¹) known to produce reversible nephropathy. Even so, it is usually avoided in patients with renal impairment.

Toxicity

- Hepatic damage may occur.

DESFLURANE

Desflurane's relatively low boiling point (23.5°C) makes it extremely volatile, however, since this temperature is close to ambient temperature in many theatre settings, full vapour saturation cannot be guaranteed if a conventional vaporizer is employed. Therefore, a Tec 6 vaporizer is used which heats the agent to 39°C at a pressure of 2 atmospheres, ensuring full vapour saturation which enables a carefully regulated amount of vapour to be added to the fresh gas flow. 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 (e.g. after neurosurgery).

Effects

Respiratory

- Similar respiratory effects to the other agents with a rise in PaCO₂ and a fall in minute ventilation. These effects are more pronounced than halothane, but less than isoflurane and enflurane.
- It has a potent odour and can cause coughing and breath holding and is not suitable for induction.

Cardiovascular

- Effects are similar to isoflurane, but in concentrations above 1 MAC, desflurane may produce tachycardia and hypertension.
- Care should be taken in patients with ischaemic heart disease. Vascular resistance falls in the cerebral and coronary circulations.

Metabolism

- Only 0.02% is metabolised.

SEVOFLURANE

Effects

Respiratory

- Ventilation is depressed in a predictable manner with a rise in PaCO₂ and a fall in minute ventilation.
- Its pleasant odour and relatively low blood:gas partition coefficient make it particularly suitable for induction.

Cardiovascular

- Heart rate and contractility are unchanged, but a fall in SVR leads to a reduction in blood pressure.
- Vascular resistance in the cerebral and coronary circulations is reduced.

Central nervous system

- There is some evidence that children exhibit a higher incidence of post operative agitation and delirium compared with halothane.

Metabolism

- Sevoflurane undergoes hepatic metabolism by cytochrome p450 (2E1) to a greater extent than all the other commonly used volatile agents apart from halothane. Hexafluoroisopropanol and inorganic

F⁻ are produced, although renal toxicity is not observed even when F⁻ plasma levels reach 50mcmol.l⁻¹.

Toxicity

When sevoflurane is administered in a circle system using soda lime or baralyme, a number of compounds are produced, named compounds A-E. Only compounds A and B are present in significant quantities. Animal studies extrapolated to humans suggest a human nephrotoxic threshold of 150-200ppm but studies have shown that even with flow rates of 0.25l.min⁻¹ for 5 hours, then the level of compound A produced peaks at less than 20ppm and is not associated with renal impairment.

ETHER (Diethyl ether)

This is an inexpensive agent made from sugar cane (ethanol) that is still used in isolated settings in some countries. It is the volatile agent of choice when general anaesthesia is needed but no oxygen is available.

Effects

Respiratory

- Ether stimulates respiration and when too much ether is given respiration becomes depressed before the heart. These effects make ether a relatively 'safe' anaesthetic agent and its continued use in some isolated settings in the developing world.
- It is a bronchodilator and may be used as the sole anaesthetic agent and is capable of producing good abdominal muscle relaxation.
- It stimulates salivation and is best used with an antisialogogue premedication
- Ether is associated with a slow onset and a slow recovery. The vapour is unpleasant to breathe initially and causes irritation of the bronchial tree which may slow down the induction of anaesthesia.

Cardiovascular

- Cardiac output and blood pressure are usually increased due to its sympathomimetic effect mediated by adrenaline release.

Other effects

- Ether has analgesic properties.
- The incidence of nausea and vomiting is higher with ether than with other agents. The frequency is related to the concentration of ether used and is lower when ether is given via an endotracheal tube during relaxant anaesthesia.
- Ether causes little uterine relaxation and it is especially useful for caesarean section (because the baby tolerates it and the uterus contracts well). It is better avoided in moderate or severe pre eclampsia because of its sympathomimetic activity.

Adverse effects

Ether is explosive when mixed with oxygen and is inflammable in air. It may be ignited by a flame or an electrical spark such as those produced by diathermy or static electricity. The ether vapour is inflammable within the patient (lungs, airway or stomach full of vapour) or outside the patient within 25cm of the anaesthetic circuit. Scavenging must always be carried out (where possible) to avoid contact between heavy

inflammable ether vapour and diathermy apparatus or other electrical devices that may spark. If the end of the scavenging tube is placed on the floor (away from any possible sources of ignition) then the heavy ether vapour will remain at floor level and the smell of the agent to the surgical and anaesthetic team reduced.

XENON

Xenon (Xe) is an inert, odourless gas that is present in minute quantities in the atmosphere and is produced by the fractional distillation of air. It has a high MAC and very low blood:gas partition coefficient resulting in a faster onset and offset of action than desflurane or N₂O. It also has

significant analgesic properties and is not metabolised. The high cost of manufacture has limited its use to mainly that of a research agent.

FURTHER READING

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- Calvey TN, Williams NE. Principles and Practice of Pharmacology for Anaesthetists, 4th edn. Blackwell Science. 2001.
- Peck TE, Hill SA, Williams M. Pharmacology for Anaesthesia and Intensive Care, 2nd edn. Greenwich Medical Media Ltd. 2003.

Table 4. Effects of inhaled anaesthetics

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Cardiovascular effects:					
Contractility	↓↓↓	↓	↓↓	minimal	↓
Heart rate	↓↓	↑↑	↑	↑↑	nil
Systemic vascular resistance	↓	↓↓	↓	↓↓	↓
Blood pressure	↓↓	↓↓	↓↓	↓↓	↓
Coronary steal	no	possibly	no	no	no
Splanchnic blood flow	↓	unchanged	↓	unchanged	unchanged
Sensitization to catecholamines	↑↑↑	nil	↑	nil	nil
Respiratory effects:					
Respiratory rate	↑	↑↑	↑↑	↑↑	↑↑
Tidal volume	↓	↓↓	↓↓↓	↓↓	↓
PaCO ₂	unchanged	↑↑	↑↑↑	↑↑	↑
Other effects:					
Cerebral blood flow	↑↑↑	↑	↑	↑	↑
Cerebral O ₂ requirement	↓	↓	↓	↓	↓
EEG	burst suppression	burst suppression	epileptiform activity	burst suppression	burst suppression
Effect on uterus	some relaxation	some relaxation	some relaxation	some relaxation	some relaxation
Potential of muscle relaxation	some	significant	significant	significant	significant
Analgesia	some	some	some	some	some