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Inhalational Anaesthetic Agents

The inhalational anaesthetic agents (AA) were the first *general anaesthetic* agents to be developed. At first, they were used as sole agents to provide all 3 components of the "triad" of anaesthesia – hypnosis, analgesia and muscle relaxation. Today, with the tendency to use separate drugs to achieve each of these objectives, the inhalational agents are combined with other drugs to deliver a "balanced" general anaesthetic. They provide the hypnotic component of the triad.

Most older agents are no longer in use, because they are either flammable (cyclopropane and ether), or toxic to the liver (chloroform) and kidneys (methoxyflurane). Those still in clinical use are:

(a) **Nitrous oxide** (N_2O), the only inorganic molecule and the only gas at room temperature;
and (b) **Halothane, enflurane, isoflurane, sevoflurane** and **desflurane**; potent halogenated agents that are volatile liquids.

Ether is still in use in some poorly resourced areas where its flammability is not an issue as it is invariably used with air in a draw-over system. Despite its unpleasant side effects, the inherent safety of ether makes it a suitable agent under these circumstances.

At room temperature the volatile agents are below their *critical temperatures* and therefore more correctly referred to as anaesthetic *vapours*, rather than *gases*. *(The critical temperature of a substance is the temperature above which a substance cannot be liquefied, however much pressure is applied. Above its critical temperature the substance is termed a gas.)* The terms inhalational anaesthetic agents, gases, vapours and volatiles are all used interchangeably.

Administration of inhalational agents

N_2O delivery is controlled by the **flow meter** on the anaesthetic machine. **Volatile agents** are administered via individual, specially calibrated **vaporisers**. The desflurane vaporiser has a different design to the others as this agent has a boiling point near room temperature. Vaporisers are colour-coded for safety and have specific keyed fillers. These are also colour-coded and their *tips (which insert into the vaporiser)* and *ends (which fit onto the bottle of each volatile)* are individually shaped so that you cannot put one onto the other. This is an additional safety feature.

Uses of inhalational agents

1) Use of a potent anaesthetic vapour, with or without the addition of nitrous oxide, is still the most common means of **maintaining** anaesthesia. The volatile agent, which is carried in a mixture of oxygen and air / nitrous oxide, is breathed spontaneously by the patient or delivered to the lungs via a ventilator.
2) Halothane and sevoflurane, with or without the addition of nitrous oxide, are both suitable for an **inhalational** or **gas induction**, which is often done in **children**. Inhalational inductions are also used in patients with a **compromised airway**. This is much safer than an IV induction because the patient continues to *breathe spontaneously*. With an IV induction, the patient often becomes apnoeic and the airway may be lost. During an inhalational induction, the "stages of anaesthesia" based on the clinical signs described by Guedel can be used to ensure adequacy of anaesthesia and prevent an overdose.
3) N_2O may be used to provide intra-operative and labour analgesia.
4) N_2O may be used to speed up an inhalational induction (*"second gas effect")* and its use during the maintenance phase reduces the concentration of potent volatile agent required.

Features of the ideal inhalational anaesthetic agent

1) **Cheap:** Agent, equipment and safety apparatus
2) **Stable:** Easy storage, transport, use with soda-lime, non-flammable / explosive
3) **No metabolism:** Fewer toxic effects
4) **Potent:** Allows one to use high inspired oxygen concentrations
5) **No longterm effects:** No toxicity to personnel, patients or the environment
6) **Non-irritant odour:** Pleasant smell and easy inhalational induction
7) **No respiratory depression**
8) **No cardiovascular depression**
9) **Hypnotic and analgesic**
10) **Readily reversible, neuroprotective and non-excitatory**

Pharmacokinetics: Uptake and distribution

Factors affecting inspired concentration of anaesthetic agent (F_IAA*)*

When a vaporiser is turned on, a percentage of agent is selected to be vaporised into the carrier gas flowing out from the anaesthetic machine. If 2 % of isoflurane is selected, then 2 % of the gas mixture that leaves the machine to enter the breathing circuit is isoflurane vapour. However, the patient may not necessarily receive the concentration set on the vaporiser, as may be observed on the monitor's agent analyser. The composition of the gas mixture that the patient inspires (F_IAA) will depend on:

(a) the *volume of the breathing circuit*,
(b) the *fresh gas flow rate*
and (c) any *absorption of inhalational agent by the breathing circuit.*

Factors affecting alveolar concentration of anaesthetic agent (F_AAA*)*

Alveolar concentration (F_A) is directly proportional to the alveolar partial pressure, which determines the partial pressure of the AA in blood and, ultimately, in the *brain*, where it has its *clinical effect*. Factors increasing alveolar anaesthetic concentration speed up induction of anaesthesia, whereas factors that decrease alveolar concentration slow it down. The three major determinants are:

1) **Inspired concentration:** Increasing the inspired concentration (F_I) not only increases the alveolar concentration but also the rate of its rise, and hence the speed of induction.

2) **Uptake:** The alveolar concentration, which is measured by the agent analyser as the end-tidal value, is initially less than the F_I because there is *uptake* of the anaesthetic agent from the alveoli by the patient's pulmonary circulation.
The greater the uptake, the slower the rate of induction.

   The anaesthetic uptake depends on:

   a) **Solubility of the agent in the blood (blood : gas partition coefficient – BGPC)**
   The BGPC at a certain temperature is defined as the ratio of the amount of volatile present in the blood compared with the alveolar gas, the two phases (blood and gas) being of equal volume and at equilibrium. This value gives an indication of the agent's solubility in the blood. More soluble agents, e.g. halothane (BGPC = 2,3), are slower induction agents as large quantities are removed from the lungs by the circulation, causing low alveolar partial pressures (P_AAA) and a slow rise in arterial and brain partial pressure. By comparison, sevoflurane (BGPC = 0,6) is much less soluble and results in a more rapid induction.

   b) **Cardiac output (CO)**
   Increased CO results in increased AA uptake from the alveoli by the blood. This slows the rate of rise of the alveolar partial pressure and hence slows the rate of induction.

   c) **Alveolar to mixed venous partial pressure difference**
   This gradient depends on the amount of AA removed by the tissues. During induction, the tissues remove a large portion of AA as there is a big concentration gradient between the blood and tissues. Therefore mixed venous blood concentration returning to the lungs is low and uptake into pulmonary capillary blood is high. At equilibrium (which may take hours) there is no difference between partial pressures in the alveoli and returning mixed venous blood and so the uptake of AA is zero. The *uptake by the tissues* depends on *tissue solubility*, *tissue blood flow* and the *concentration gradient* between the blood and the tissues. Initially, the greatest uptake is by the *vessel-rich group* of organs receiving the largest fraction of the CO (liver, kidneys, heart and brain). Once equilibrium is reached in this group; the *muscle group* uptake will equilibrate in 1 - 3 hours; and finally the *vessel-poor* adipose tissue will take many hours to reach equilibrium, but contributes a greater proportion of the total uptake as it is a large proportion of body weight.

3) **Alveolar ventilation:** Induction is accelerated by hyperventilation, which has the effect of constantly replacing the alveoli with AA that is being taken away by the pulmonary blood flow. Induction is slowed by hypoventilation, as with respiratory depression or airway obstruction.

Factors affecting arterial concentration of anaesthetic agent (F_aAA*)*

We assume that the partial pressure of the AA is the same in the systemic arterial blood as in the pulmonary capillaries, but this is not always the case. When there is **shunting** of some pulmonary blood past non-ventilated alveoli, then blood cannot absorb AA and effectively this dilutes the non-shunted volume of blood. This lowers the arterial concentration and slows induction. Shunts may be *intra-pulmonary* (atelectasis, bronchial intubation) or *intra-cardiac* (ASD, VSD, Fallot's tetralogy).

Pharmacokinetics: Metabolism and elimination

Recovery from anaesthesia

Elimination of AA occurs mainly through the alveolus and so the same factors that speed up induction also speed up recovery. Recovery is rapid following anaesthesia with poorly soluble agents (desflurane, sevoflurane and nitrous oxide), and slow for highly soluble agents (halothane). Anaesthetic depth can also be more rapidly controlled with the poorly soluble agents.

Metabolism of inhalational agents

Volatile agents are rapidly removed from the body via the lungs and this is the most important route of their elimination. However, they are also metabolised in the liver by the cytochrome P-450 group of enzymes to a varying degrees. Some metabolites may be harmful.

Potency of inhalational agents

The potency of individual inhalational agents is compared by looking at their MAC values.

Minimum Alveolar Concentration (MAC)

MAC is defined as the steady-state minimum alveolar concentration at sea level (i.e. 1 atmosphere pressure) that prevents movement to a standard surgical stimulus (skin incision) in 50 % of non-premedicated adults.

Sometimes referred to as the MAC_{50}.
MAC_{95} (i.e. where 95 % of adults will not respond) is usually 1,3 x MAC_{50}.

Agents with *low potency*, e.g. desflurane (MAC = ± 6), require a higher alveolar concentration to achieve a comparable level of anaesthesia to those with *high potency*, e.g. halothane (MAC = 0,75). MAC values are related to fat solubility (oil **:** gas partition coefficients). Brain is very fatty tissue! Halothane has the highest fat solubility and is the most potent of the inhalational agents.

MAC allows us to predict the required anaesthetic dose for a patient.
In the clinical situation, 1,3 x MAC of any agent will provide surgical anaesthesia in the majority of patients (95 %).
MAC's are additive: 0,6 MAC of N_2O + 0,7 MAC of halothane = 1,3 MAC worth of anaesthetic effect.

MAC_{Awake} is the average of the concentrations immediately above and below those permitting voluntary response to command. For isoflurane, desflurane and sevoflurane, MAC_{Awake} is about 30 % of MAC, while for halothane MAC_{Awake} is more than 50 %- and for N_2O more than 60 %- of MAC.

Another "MAC" is **MAC_{BAR}**, the alveolar concentration that **B**locks **A**utonomic **R**esponse to surgical stimulation. This is higher than MAC and varies with various agents. MAC_{BAR} is significantly lowered by opiates.

Factors altering MAC	
↑ MAC	**↓ MAC**
Infancy	Neonates
	Elderly
	Pregnancy
	Hypotension
Hyperthermia	Hypothermia
Hyperthyroidism	Hypothyroidism (myxoedema)
Catecholamines and sympathomimetics	α_2 agonists
	Sedatives
Chronic opioid use	Acute opioid use
Chronic alcohol intake	Acute alcohol intake
Acute amphetamine intake	Chronic amphetamine intake
	Lithium
Hypernatraemia	

Factors which do NOT affect MAC: Gender, duration of anaesthesia, time of day, hypocarbia.

But beware the redhead! ☺ Patients with red hair are reputed to require up to 20 % more anaesthetic for the same level of anaesthesia.

The inhalational anaesthetic agents

1) Nitrous oxide (N_20): Cylinder & pipeline colour – Blue **MAC = 105 %**

Nitrous oxide (the only gas and not a volatile agent, as the other agents are) is commonly used in general anaesthesia, and also known as "laughing gas". It is stored as a *liquid* in "**french-blue**" cylinders. Pressure gauges cannot be used to measure the amount left in the cylinder, as the pressure above the liquid remains constant until no more liquid remains; at this point the pressure drops suddenly. The volume of gas remaining may be determined by weighing the cylinder. N_2O is non-explosive but, like oxygen, strongly supports combustion. It is prepared commercially by heating ammonium nitrate and removing impurities.
It is a potent analgesic but poor anaesthetic, especially at higher altitudes where greater concentrations of oxygen are required. An inspired concentration > 80 % N_2O would be a dangerous *hypoxic mixture* of gases. To be safe, a maximum of 70 % N_2O (i.e. O_2 = 30 %) is advised and this is insufficient for reliable anaesthesia (< 1 MAC). However, N_2O is frequently used as a carrier gas to deliver the volatile agents. It is also useful in reducing the concentration of volatile needed. It is pleasant-smelling and induction is rapid. The "second gas effect" refers to the theoretical ability of N_2O to speed up an inhalational induction with another volatile agent.

Entonox® is a mixture of 50 % N_2O and 50 % O_2: Used for analgesia in labour and minor emergency room procedures, such as manipulation of fractures and suturing. Often carried by ambulances.
It is administered by a hand-held demand-valve.

Side effects: CVS depression due to negative inotropy when used with high dose opiates. It augments the respiratory depression effects of induction agents and opiates. N_2O diffuses into *air-filled spaces* and the nitrogen (N_2) in this space diffuses out much slower as it has a lower BGPC, with resultant *rapid expansion* of these air-filled spaces: Pneumothorax, pneumomediastinum, pneumocephalus, etc., may be aggravated. This may also be a problem in bowel-, middle ear- and eye- surgery.

Diffusion hypoxia: At the end of an anaesthetic when the N_2O is switched off, it rapidly diffuses in large amounts back from the blood into the alveoli in those first few minutes after its discontinuation. The partial pressure of O_2 in the alveoli drops, as it becomes diluted by the N_2O. Theoretically, a patient could develop what is known as *diffusion hypoxia.* In young fit patients with healthy lungs there should be no detectable effect. However, it is considered safe practice to administer a higher F_{IO_2} of 0,4 - 0,8 (40 - 80 % O_2) for 5 - 10 $\min$ after N_2O has been switched off.

Toxic effects: It is a cause of postoperative nausea and vomiting (PONV). If given for long periods it may cause bone marrow depression. The alleged increased incidence in 1st trimester miscarriage in female theatre staff from long-term low-grade exposure has not been proven. It is addictive. Vents into the atmosphere and is the 3rd most abundant greenhouse gas (after CO_2 and methane).

2) Halothane: Colour code – Red **MAC = 0,75 %**

Halothane was the first of the modern halogenated agents to be used. Chemically a halogenated hydrocarbon, it is a colourless liquid that is decomposed by light and must be stored in amber bottles with 0,01 % thymol as a stabiliser. Non-flammable and non-explosive. It is non-irritant and most patients find its characteristic smell reasonably pleasant. Use 1 - 2 % for induction, and lower concentrations for maintenance, e.g. 0,5 - 0,75 %.

Organ effects:

CNS: *Potent* anaesthetic. It increases cerebral blood flow and intracranial pressure, which may be minimised by hyperventilation. Slow recovery, with a noticeable "hangover" effect.

CVS: Causes *hypotension* due to myocardial depression and vasodilatation. *Dysrhythmias*, especially sinus bradycardia and nodal rhythm are common and dose-related. It sensitises the heart to catecholamines.

Respiratory: A respiratory depressant, it increases rate but decreases tidal volume (V_T).
It is a good *bronchodilator* (as are all the other volatile agents).

Skeletal muscle: Produces some *muscle relaxation*. A trigger for *malignant hyperthermia (MH).* (As are all inhalational agents, except N_2O).

Uterus: *Uterine relaxation* and risk of bleeding if used in high concentration during caesarean section.

Liver: Mild elevation in liver enzymes is common postoperatively.
A rare complication is "*halothane hepatitis*" (1 in 35 000 cases); an idiosyncratic allergic phenomenon which results in fulminant hepatic necrosis with a 50 - 75 % mortality.
Significant amounts of halothane are metabolised in the liver and excreted over many days.

3) Isoflurane: Colour code – Purple **MAC = 1,2 %**

Colourless halogenated ether. Less potent than halothane, but currently the most widely used inhalational agent at GSH (and probably worldwide), as the cost has decreased. There is a faster recovery compared with halothane and there is no risk of fulminant hepatitis.

Organ effects:

Respiratory: Vapour is irritant to the airways, so inhalational induction is not recommended. Slightly more of a respiratory depressant than halothane.

CNS: Least effect on cerebral blood flow and intracranial pressure of all the agents, therefore agent of choice in *neuro-anaesthesia*. More *rapid recovery* from anaesthesia compared with halothane.

CVS: Minimal myocardial depression and no sensitisation to catecholamines. A good peripheral vasodilator, causing a drop in blood pressure. There was a concern about its use in patients with coronary artery disease because of a theoretical possibility of *"coronary steal" – The theory states that by dilating normal arteries, blood could be diverted away from areas of myocardium supplied by stenotic arteries.* This effect is probably not clinically relevant.
Pulse rate is maintained, with a tendency to tachycardia in young patients.

Liver: Low potential for toxicity, but isolated reports of enzyme elevation. Reduces total hepatic blood flow, but preserves hepatic arterial blood flow, so *best* agent for patients with *liver disease*.

Skeletal muscle: *Relaxant*; potentiates non-depolarisers. Also precipitates *malignant hyperthermia* in common with all the volatile agents.

Uterus: *Relaxation*, but less so than halothane.

Eye: Produces good operative conditions.

4) Sevoflurane: Colour code – Yellow **MAC = 2 %**

A fluorinated derivative of methyl isopropyl ether. Sevoflurane is a relatively *weak* volatile agent, but this is compensated for by its low solubility, which facilitates fast induction, changes in depth and recovery from anaesthesia. It is the most popular agent for inhalational inductions because it is pleasant to inhale and has a rapid onset. Muscle rigidity on induction, and emergence delirium sometimes occur. It is probably the most widely used agent in the "first world", but is still expensive.

Organ effects:

CNS: Similar to isoflurane and desflurane.

CVS: Mild myocardial depression; decreases SVR less than isoflurane and no effect on heart rate. May prolong the q-T interval on ECG. Does not sensitise the myocardium to catecholamines and does not induce dysrhythmias. It is possibly the agent of choice for cardiac patients.

Respiratory: Similar to halothane and isoflurane. It is non-irritant and a bronchodilator.

Toxicity: 3 - 5 % metabolised in the liver, with release of inorganic *fluoride*, but not in sufficient quantities to cause renal failure. *Compound A* is a potentially nephrotoxic end product found with exposure to soda lime in circle systems, but has no clinical significance at normal concentrations. Some countries limited fresh gas flows to > 2 $l\ min^{-1}$ with sevoflurane to minimise the accumulation of compound A, but there is no evidence to support this.
It should probably be used with caution or avoided in patients with established renal failure.

5) Desflurane: Colour code – Sky blue **MAC = 6 %**

Desflurane is the newest volatile agent, synthesised in 1993. It is expensive and needs a sophisticated vaporiser for administration. Structurally it is a fluorinated methyl-ether very similar to isoflurane. It is non-flammable and non-explosive, like the other agents, and very stable in soda lime, which is fortunate, as its high cost necessitates the use of a closed system. It undergoes minimal biotransformation, so its toxic potential is very small. It produces rapid induction, but is extremely irritant and unpleasant and therefore not used for inhalational inductions. Recovery is faster than with all the others because it is the most insoluble agent. Depth of anaesthesia can be rapidly and sensitively controlled. CVS, respiratory and CNS effects are similar to isoflurane. Rapid increases in desflurane concentration can lead to short-lived but marked increases in heart rate, blood pressure and catecholamine levels. It has been associated with the production of toxic concentrations of carbon monoxide (CO) when exposed to desiccated (dry) soda lime under certain circumstances.

6) Enflurane: Colour code – Orange **MAC = 1,7 %**

Enflurane is practically obsolete, as it has been replaced by more modern agents. It has unacceptable side effects. At high concentrations it may provoke epileptiform activity on the EEG, which is why it is avoided when anaesthetising epileptic patients! It is also contra-indicated for neurosurgery, as it raises intracranial pressure; and in renal failure. It also became very expensive.

Properties of commonly used anaesthetic agents

	Nitrous oxide	Halothane	Isoflurane	Sevoflurane	Desflurane
Structure		halogenated alkane	halogenated ether	halogenated ether	halogenated ether
Colour code	french blue	red	purple	yellow	sky blue
% Metabolised	0,004	20	0,2	3 - 5	0,02
MAC (%) in O_2	105	0,75	1,2	2	6
BGPC	0,45	2,3	1,4	0,6	0,42
Flammability	non-flammable, but allows combustion	non-flammable	non-flammable	non-flammable	non-flammable
Cardiovascular effects					
BP	↔	↓↓	↓↓	↓	↓↓
HR	slight ↓	↓	↑	↔	↔ or ↑
SVR	slight ↑	↔	↓↓	↓	↓↓
CO	slight ↓	dose-dependent ↓	↔	slight ↓	↔ or ↓
Respiratory effects					
PVR	↑	↔	↔	↔	↔
V_T	↓	↓↓	↓↓	↓	↓
RR	↑	↑↑	↑	↑	↑
P_aCO_2	↑	↑	↑	↑	↑↑
Airway irritation	No	No	Yes	No	Yes
Bronchodilation	↔	↑↑	↑	↑	↑
Cerebral effects					
Blood flow	↑	↑↑	↑	↑	↑
ICP	↑	↑↑	↑	↑	↑
$CMRO_2$	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Neuromuscular effects					
Nondepolariser	↑	↑↑	↑↑↑	↑↑	↑↑↑
MH trigger	No	Yes	Yes	Yes	Yes
Renal effects					
Blood flow	↓↓	↓↓	↓↓	↓	↓
GFR	↓↓	↓↓	↓↓	?	?
UO	↓↓	↓↓	↓↓	?	?
Hepatic effects					
Blood flow	↓	↓↓	↓	↓	↓