Inhalational anaesthetic agents

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Abstract

The continued development of anaesthetic agents since the late 18th century has paved the way for the progression of surgical techniques. Inhalational agents are used worldwide for the delivery of safe, effective anaesthesia. These include the volatile agents halothane, isoflurane, sevoflurane and desflurane, in addition to the anaesthetic gases nitrous oxide and xenon. Although the newer volatiles have an improved safety profile in comparison to older agents, the ideal anaesthetic agent remains elusive. It is vital for anaesthetists to understand the physical properties, pharmacodynamics and pharmacokinetics of the individual inhalational anaesthetic agents so that the most appropriate agent for a patient or procedure is selected and administered correctly.

Keywords Anaesthesia; anaesthetic agents; general; inhalational; minimum alveolar concentration

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- understand the current theories of mechanism of action of inhalational anaesthetic agents
- describe the factors influencing the speed of onset of, and emergence from, inhalational anaesthesia
- list the uses, presentation, physiochemical properties, effects, pharmacokinetics and pharmacodynamics of the commonly used inhalational agents

Introduction

Prior to the 18th century, attempts to alleviate the pain of illness, injury or for simple surgical techniques predominantly relied upon either the ingestion of ethanol and herbal mixtures, or blows to the head and carotid artery massage.[1] Although the analgesic and amnesic properties of both nitrous oxide and ether were known by the late 1700s, their clinical potential was largely overlooked in favour of their recreational use. It was not until the famous ether demonstration by William Morton at Massachusetts General Hospital in 1846 that the modern concept of anaesthesia using inhalational agents was born.

Inhalational and volatile agents are now widely used for the induction and maintenance of general anaesthesia. Early agents such as diethyl ether, chloroform, ethyl chloride, cyclopropane and trichloroethylene although effective, were either highly flammable or toxic. Halothane, discovered in 1951 and first used clinically in 1956, had a more favourable safety profile and marked the modern era of volatile hydrocarbons and fluorinated ethers.

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Modern inhalational anaesthetic agents

Although halothane is still in use in many low- and middle-income countries, its adverse effect profile has largely resulted in it falling out of mainstream use in favour of the more recently discovered fluorinated ethers: isoflurane, sevoflurane, and desflurane. The noble gas, xenon, has demonstrated impressive anaesthetic and analgesic properties; however, it is an extremely rare element (1 part per 20 million in the Earth's atmosphere) and its clinical use is therefore currently limited by significant production costs. The search for the ideal anaesthetic agent (Box 1) continues, with no inhalational agent currently available meeting these demanding criteria. Volatile anaesthetic agents are delivered to the patient via a 'carrier gas' mixture. This is most commonly a combination of air/oxygen or oxygen/nitrous oxide (N_20).

Mechanism of action

Despite being used widely in clinical practice for over 170 years, the exact mechanism by which the volatile anaesthetic agents act is still largely unknown. They belong to a diverse group with no recognizable or unifying chemical class.

Macroscopically, volatile anaesthetic agents prevent both the transmission of noxious stimuli ascending in the spinothalamic tracts to the thalamus and subsequently the cortex, in addition to a neuronal response to pain at a spinal level. Hypnosis and amnesia most likely result from direct supraspinal depression, particularly of the thalamus and reticular formations.[2]

At a molecular level, there are two main theories of action.[3]

Lipid theory or Meyer–Overton correlation

In the early 1900s both Meyer and Overton noticed a linear relationship between log minimum alveolar concentration (MAC) (measure of potency, see Box 2) and lipid solubility. The more soluble a volatile anaesthetic (represented by a higher log oil:gas partition coefficient), the more potent the agent is (lower log MAC) (Figure 1). This led to the theory that volatile anaesthetic agents caused interruption of the usual function of the cell membrane lipid bilayer by penetration and disruption of the molecular arrangement of phospholipids and ion channels. The more soluble an agent, the more disruption to the membrane at lower doses. Although once popular, this theory has largely been dismissed in favour of the more popular 'protein theory'.

Properties of the ideal inhalational anaesthetic agent

Physical

- Stable compound without need for preservatives
- Sufficiently high saturated vapour pressure to allow easy vaporization
- Non-flammable/does not support combustion
- Does not interact with anaesthetic equipment (rubber, plastic, glass, metals, soda lime)
- Cheap to manufacture
- Easy to store with long shelf-life
- Production and/or use is not associated with environmental damage/pollution
- Easy to administer
- Easily scavenged
- Non-irritant to the respiratory tract and non-pungent to allow gaseous induction

Pharmacological

- Minimal/no metabolism and excreted unchanged by lungs (i.e. not influenced by hepatic or renal impairment/disease)
- Low blood:gas coefficient to facilitate rapid onset/offset of anaesthesia
- High oil:gas coefficient to ensure high potency
- No toxic effects (e.g. allergic reactions, teratogenicity, carcinogenesis)
- No interaction with other anaesthetic agents/drugs
- Does not trigger malignant hyperthermia
- No adverse effects on other organ systems:
  - *Cardiovascular*: no cardiovascular depression; does not cause coronary steal
  - *Respiratory*: *does* not depress respiratory rate; bronchodilator
  - *Central nervous system*: analgesic properties; no effect on cerebral autoregulation or cerebral blood flow; non-epileptogenic; provides muscle relaxation
  - *Gastrointestinal*: antiemetic properties
  - *Genitourinary*: no effect on uterine tone

Box 1

Protein theory

There is increasing evidence that anaesthetic agents exert their effect by inhibiting excitatory (serotonergic, neuronal nicotinic and N-methyl-D-aspartate (NMDA)) and activating inhibitory (γ-aminobutyric acid $(GABA)_A$ and glycine) ion channels that are distributed throughout the central nervous system (CNS). This results in the pre-synaptic inhibition of neurotransmitters and/or a reduction post-synaptic response thresholds.

$GABA_A$ is a pentameric, ligand-gated ion channel spanning the phospholipid bilayer and comprising two alpha, two beta and one gamma subunit. Volatile anaesthetic agents are thought to activate the ion channel by binding to the alpha subunits causing

Minimum Alveolar Concentration (MAC)

Definition: The MAC of an agent is a measure of potency of an inhalational anaesthetic agent and is effectively its ED50 (that is, the administered dose that produces an effect in 50% of the population)

1 MAC is defined as:

'The minimum concentration of an inhalational anaesthetic agent in the alveoli, at equilibrium, at a pressure of one atmosphere, in 100% oxygen, which produces immobility in 50% of unpremedicated adult subjects when exposed to a standard noxious stimulus'*

*In clinical practice end-tidal concentration of an inhalational anaesthetic agent is used to approximate alveolar concentration and is used as a crude guide for depth of anaesthesia.

Thus 1 MAC sevoflurane is equal to 1 MAC desflurane. However, due to their differing potencies (oil:gas partition coefficients) sevoflurane requires an alveolar concentration of around 2% and desflurane around 6% to achieve 1 MAC (in air/oxygen).

Although 1 MAC sevoflurane is equal in potency to 1 MAC desflurane, it does not follow that the agents are equipotent at 2 MAC. However, in general terms, 0.5 MAC of one inhalational anaesthetic agent in combination with 0.5 MAC of another agent approximates to 1 MAC in total.

MAC awake (MAC_{aw})

This term was coined in 1970. It is defined as the alveolar concentration of an agent that is midway between that permitting response to command and that preventing it. For the modern volatile inhalational anaesthetic agents it is around 0.3 MAC.[4]

MAC_{bar}

This is defined as the brain concentration of agent which blocks adrenergic responses to skin incision. Unlike MAC_{aw}, it varies between agents. Desflurane and isoflurane have MAC_{bar} around 1.3 MAC whereas for sevoflurane it is 3.5 MAC.[4] These values are decreased with the co-administration of opioid analgesic drugs.

Factors affecting MAC

There are several factors that can affect the alveolar concentration required to achieve 1.0 MAC of a delivered inhalational anaesthetic agent

Increased MAC

- Age (peak MAC value is at six months)
- Hyperthermia
- Hypernatraemia
- Thyrotoxicosis
- Elevated CNS catecholamines: stress/anxiety states
- Chronic alcohol or opioid use

Decreased MAC

- Acute ingestion of alcohol or CNS depressant drugs
- Increasing age
- Pregnancy
- Hypothermia
- Hypotension
- Hypothroidism
- Hyponatraemia

Box 2

Meyer–Overton correlation between inhalational anaesthetic agent potency (minimum alveolar concentration, MAC) and oil:gas partition coefficient using logarithmic scales

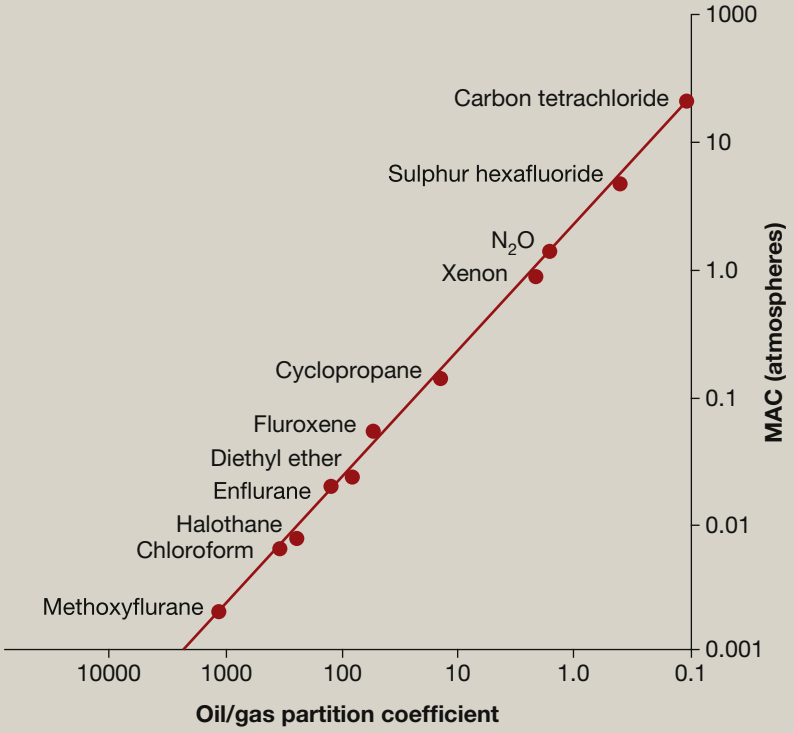

Figure 1

a conformational change resulting in increased chloride conductance and thus hyperpolarization of the cell membrane. Recently discovered potassium channels, thought to be responsible for setting the resting membrane potentials of pre- and post-synaptic membranes in the CNS, are also thought to be a site of action for the volatile agents.

The relationship between lipid solubility and potency can be explained by the lipophilic nature of the specific binding sites on the ion channels.

Kinetics of inhaled anaesthetic agents

Inhalational anaesthetic agents exert their CNS effects via direct action on the brain and spinal cord resulting in hypnosis (loss of consciousness), antinociception and muscle relaxation. The extent of the response is related to the partial pressure of the anaesthetic at the effect site, in this case the brain (P_{brain}). As this is not directly measurable, it is assumed that, at steady state, P_{brain} is in equilibrium with the partial pressure of the inhalational agent in arterial blood ($P_{arterial}$) which is in turn in equilibrium with the partial pressure of the agent in the alveolus ($P_{alveoli}$). The alveolar pressure is usually approximated to the end-tidal concentration of inhalational agent ($P_{end\text{-}tidal}$) which is easily measured in expired breath. Steady state is rarely achieved in the clinical setting even with modern agents as the process can take many hours.

$$P_{brain} \rightleftarrows P_{arterial} \rightleftarrows P_{alveoli} \rightleftarrows P_{end\text{-}tidal}$$

Onset of anaesthesia is related to effect-site concentration and therefore the speed of onset of anaesthesia is related to speed of delivery of inhalational agent to the CNS. This is influenced by factors affecting both the alveolar concentration of inhalation anaesthetic agents and drug uptake from the lungs.

Alveolar concentration of inhalational agents

Inspired agent concentration (Figure 2): delivery of high inspired concentrations (F_I) of an anaesthetic agent will increase the speed of anaesthetic onset. This results from the creation of a large concentration gradient of inhalational agent between the alveolus (F_A) and arterial blood. High F_A/F_I ratios will favour rapid diffusion across the alveolar membrane and therefore faster delivery to, and onset at, the effect site. The F_I will be affected by the chosen vaporizer output, breathing circuit fresh gas flow, breathing system volume/design and circuit absorption.

Alveolar ventilation: increased alveolar ventilation will result in a more rapid onset of anaesthesia by maintaining a concentration gradient across the alveolar membrane.

Functional residual capacity (FRC): patients with a greater FRC will experience a slower onset of anaesthesia. This is due

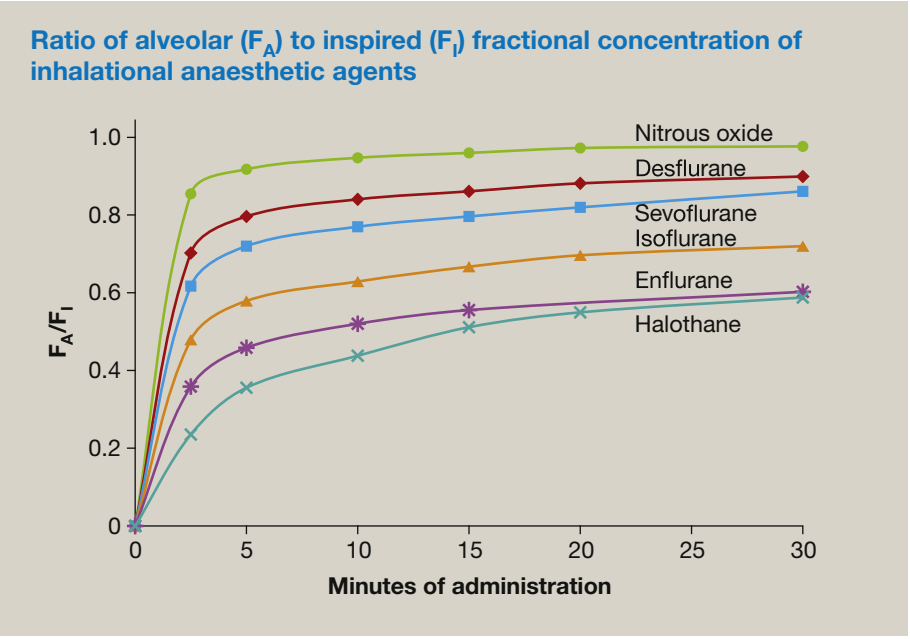

Figure 2

to the dilution effect of air within the FRC on the concentration of the inspired inhalational agent and subsequent flattening of the concentration gradient between the alveolus and arterial blood.

Drug uptake from the lungs

Blood:gas partition coefficient: the blood:gas partition coefficient is a measure of the solubility of an inhalational anaesthetic agent in blood. It is defined as the ratio of the amount of an anaesthetic agent in blood and gas when the two phases are of equal volume and pressure and in equilibrium at 37°C. The more soluble an agent, the longer it takes for the partial pressure of the agent in blood to rise due to a slower increase in F_A/F_I ratio. As previously described, it is the partial pressure of the agent at the effect site that is related to anaesthetic onset, not total blood content. Hence the more soluble an agent in blood (higher blood:gas partition coefficient), the slower the onset of anaesthesia. Use of more soluble agents will also result in a slower recovery from anaesthesia due to a greater volume of distribution (Box 3).

Second gas effect: this is a description of the phenomenon of a more rapid onset and offset of anaesthesia when a volatile anaesthetic agent is co-administered with N_2O. Nitrous oxide is around 20 times more soluble in blood than oxygen or nitrogen and is rapidly absorbed across alveolar membranes. This means that at high inspired concentrations of N_2O, a greater volume of

Clinical applications of the blood:gas partition coefficient

Obese patients will experience slower onset of, and emergence from, anaesthesia. This is due to a prolonged time to equilibration after induction and a longer time to emergence due to slow, prolonged release of agent from the creation of a larger depot in fatty tissue. The use of less soluble agents with lower blood:gas partition coefficients will be beneficial in this patient group.

Blood:gas partition coefficients are increased by serum constituents such as albumin, cholesterol, globulin and triglycerides. Infants and older patients with lower levels of these constituents will experience more rapid onset of anaesthesia.

Box 3

Clinical applications of the second gas effect

Induction

During inhalational induction, if N_2O is co-administered with oxygen and a volatile anaesthetic agent the speed of onset will be more rapid than if the volatile agent is delivered in an air/oxygen mixture.

Diffusion hypoxia

This occurs during emergence from anaesthesia when inspired N_2O ceases. As a result of the concentration effect N_2O will diffuse back into the alveolus down its concentration gradient from the pulmonary blood faster than nitrogen and oxygen will be leaving the alveolus. If a high fractional inspired (F_I) concentration of oxygen is not delivered, the fractional alveolar concentration (F_A) of N_2O will be increase resulting in hypoxia.

Box 4

Properties of the volatile anaesthetic agents halothane, isoflurane, sevoflurane and desflurane

	Halothane	Isoflurane	Sevoflurane	Desflurane
Uses	1 Induction and maintenance of general anaesthesia	1 Maintenance of general anaesthesia 2 Treatment of severe bronchospasm	1 Induction and maintenance of general anaesthesia 2 Treatment of severe bronchospasm	1 Maintenance of general anaesthesia
Chemical	Halogenated hydrocarbon (2-bromo-2-chloro-1,1,1-trifluoroethane)	Halogenated methylether. Structural isomer of enflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether)	Polyfluorinated isopropyl methylether (fluoror-2,2,2-trifluoro-1-ethylether) Unlike the other volatile agents, Sevoflurane is achiral.	Fluorinated methylethylether (1,2,2,2-tetrafluoroethyl difluoromethyl ether)
History	Synthesized in 1951 and first introduced into clinical practice in the UK in 1956. First of the 'modern' volatile agents. Remains the standard to which new volatiles are compared	First synthesized in 1965 and first used clinically in 1980 due to early concerns about carcinogenesis	First synthesized in 1968. Development slowed initially due to apparent toxic effects and problems with biotransformation and stability with soda lime. Available for clinical use since 1990	First used in humans in 1988, introduced into clinical practice in 1993
Presentation and storage	• Clear, colourless liquid • Sweet smell • Prepared with 0.01% thymol — prevents decomposition on exposure to light	• Clear, colourless liquid • Pungent odour • Amber coloured bottles	• Clear, colourless liquid • Pleasant smell • Stored in amber coloured polyethylene napthalate bottles with an added concentration of 300 ppm of water to prevent attack by Lewis acids and release of toxic hydrofluoric acid	• Clear, colourless liquid • Protected from light in amber coloured bottles • Ethereal and pungent odour • Requires specialised vaporizer (TEC-6) heated to 39°C and pressurized to 2 atm. This is because desflurane has a boiling point close to room temperature and a high SVP. Small temperature/pressure changes would result in a variable output from a standard vaporizer.
Physical properties	• Non-flammable • MW 197 • BP 50.2°C • SVP at 20°C 32.3 kPa • MAC 0.75 in air • Blood:gas partition coefficient 2.5	• Non-flammable in clinical concentrations • MW 184.5 • BP 48.5°C • SVP at 20°C 33.2 kPa • MAC 1.15 in air • Blood:gas partition coefficient 1.4	• Non-flammable • MW 200.1 • BP 58.5°C • SVP at 20°C 22.7 kPa • MAC 1.7—2 in air • Blood:gas partition coefficient 0.6	• Non-flammable in clinical concentrations • MW 168 • BP 23.5°C • SVP at 20°C 22.7 kPa • MAC 5—7 in air • Blood:gas partition coefficient 0.45
Uptake and distribution	• Oil:gas partition coefficient 220	• Oil:gas partition coefficient 97	• Oil:gas partition coefficient 52	• Oil:gas partition coefficient 29
Metabolism and excretion	• 20% administered dose is metabolized in the liver (CYP 2EI) by oxidation and dehalogenation • 60—80% excreted unchanged by the lungs. Metabolites excreted in urine	• 3—5% administered dose is metabolized in the liver (CYP 2E1) by the process of defluorination • 95% excreted unchanged by the lungs. Metabolites excreted in urine • Fluoride concentrations may increase significantly in presence of CYP 2EI activity. No clinical significance	• 5% administered dose is metabolized by defluorination in the liver (CYP2EI) to hexafluoroisopropanol (HFIP), carbon monoxide and inorganic fluoride. Although HFIP is potentially hepatotoxic, it is conjugated and excreted in the urine rapidly enough that it is clinically insignificant	• Only 0.02% of administered dose is metabolized to trifluoroacetic acid

MW, molecular weight; SVP, saturated vapour pressure, MAC, minimum alveolar concentration

Table 1

Cardiovascular effects of inhalational anaesthetic agents

	Halothane	Isoflurane	Desflurane	Sevoflurane
Cardiac output	reduced	reduced	stable/ reduced	stable/ reduced
Heart rate	reduced	increased	increased	stable
SVR	stable	reduced/stable	reduced	reduced
MAP	reduced	reduced	reduced	reduced

SVR, systemic vascular resistance; MAP, mean arterial pressure.

Table 2

N_2O is leaving the alveolus compared to oxygen or nitrogen entering. This results in two phenomena which are of clinical importance (Box 4).

Concentration effect – as N_2O is rapidly absorbed, the alveolar volume decreases which causes an increase in the fractional concentration of other gases in the alveolus. This increase in fractional alveolar concentration leads to an increased concentration gradient and favours faster onset and offset of anaesthesia if N_2O is co-administered with a volatile agent.

Augmentation of alveolar ventilation – the rapid absorption of N_2O results in loss of alveolar volume creating a pressure/volume gradient between the alveolus and the conducting airways. This causes augmentation of alveolar ventilation by drawing inspired gas down its pressure gradient.

Cardiac output: an increased cardiac output state (e.g. children, sepsis) results in a slower onset of inhalational anaesthesia. This is due to the rapid uptake of the inhalational agent across the capillary membrane thereby lowering the F_A/F_I ratio. Lower cardiac output states (e.g. older patients, cardiac disease) enable the maintenance of a high F_A/F_I ratio and, therefore, faster induction of anaesthesia.

Systemic effects of the individual inhalational agents in current clinical use

Inhalational volatile agents in current clinical use include sevoflurane, desflurane and isoflurane. Halothane is included as it is still used in some low- and middle-income countries and remains the volatile agent to which all new inhalational agents are compared.

The physical properties and pharmacokinetics of each of the individual inhalational agents are summarized in Table 1.[5]

Cardiovascular effects

All volatile anaesthetic agents cause a decrease in blood pressure. This is due to a combination of reduction in systemic vascular resistance (SVR) and myocardial contractility and/or cardiac output; the contribution of each element varies slightly between the individual agents and is dose dependent (Table 2). Halothane has less of an effect on SVR than the newer volatile agents. Heart rate may be preserved (sevoflurane), increased (desflurane and isoflurane) or reduced (halothane). Sensitization of the myocardium to catecholamines (and thus making the patient prone to arrhythmias) only occurs with halothane.

Postoperative Cognitive Decline (POCD)

POCD is described as a reduction in cognitive function occurring between seven days and one year after surgery. However, both clear classification and categorization remain elusive due to limited understanding of this condition. The reported incidence of POCD in the literature varies from 11.7% in non-cardiac surgery, 22% in elective hip surgery and up to 60% in cardiac surgery.[6]
Risk factors for POCD include:

- Patient factors
  - increasing age
  - poor education
  - history of cardiovascular disease
  - pre-existing cognitive impairment
  - poor functional status
  - postoperative complications
  - alcohol excess
- Surgical/anaesthetic factors
  - type of surgery (increased risk with vascular, cardiac, orthopaedic surgery)
  - excessive depth of anaesthesia (not yet proven)

Current theories of the aetiology of POCD have suggested that inhalational anaesthetic agents cause potentiation of similar pathophysiological processes to those occurring in Alzheimer's Disease. This results in increased neuronal death and loss of synapses of cholinergic pathways in the basal forebrain region resulting in alteration in consciousness, learning and memory.

There are no known treatments for POCD and management is currently largely preventative. Patients at high risk should be informed of the potential for developing POCD during the consent process. Suggested preventative measures include:

Preoperative

- Modification of risk factors
- Controlled reduction of alcohol and smoking
- Optimization of pre-existing chronic health conditions ('pre-habilitation')
- Avoidance of prolonged fasting in immediate preoperative period
- Rationalization of medications (avoidance of polypharmacy)

Intra-operative

- Avoidance of high-risk medications (e.g. benzodiazepines)
- Use of processed EEG monitoring to prevent excessive depth of anaesthesia
- Intravenous versus inhalational versus regional anaesthesia. At present there is no conclusive evidence that one technique is superior in terms of reduction the risk of POCD
- Limited surgical time

Postoperative

- Optimization of physiological parameters (avoidance of hypoxia, hypercapnia, hypothermia)
- Normalization of electrolytes
- Optimal pain management
- Reorientation and use of sensory aids in those with deficit
- Early mobilization
- Ensure perioperative administration of usual medication

Box 5

Isoflurane (and sevoflurane to a lesser degree) has been shown to cause coronary vasodilatation, experimentally resulting in a 'coronary steal' syndrome. This, however, appears to be of minimal clinical significance.

Respiratory effects

All volatile anaesthetic agents cause a dose-dependent decrease in tidal volume, decreased ventilatory response to hypoxia and hypercapnia, and inhibition of hypoxic pulmonary vasoconstriction. There is a slight simultaneous, compensatory increase in respiratory rate, but overall minute ventilation remains reduced. Respiratory depression is more marked with desflurane. Sevoflurane and halothane have relatively pleasant odours and are non-irritating to the upper respiratory tract; these volatile agents may, therefore, be used for gaseous induction. Isoflurane and desflurane are irritating to the upper respiratory tract. Sevoflurane, halothane and isoflurane all cause bronchial smooth muscle relaxation and reduction in bronchial secretions. This effect is often exploited in the management of status asthmaticus.

Central nervous system effects

All volatile anaesthetic agents cause dose-dependent depression of cerebral activity and produce general anaesthesia without lowering seizure threshold. Dose-dependent cerebrovascular dilatation also occurs, resulting in increased cerebral blood flow and intracranial pressure. This effect is thought to be less marked with sevoflurane, especially with concentrations of <1.5 MAC where cerebral autoregulation is thought to be preserved.

None of the volatile agents in current anaesthetic use demonstrate analgesic properties.

All inhalational agents have been implicated as risk factors in the development of postoperative cognitive decline (Box 5).

Gastrointestinal and genitourinary effects

All volatile anaesthetic agents cause dose-dependent uterine muscle relaxation and are a contributing factor to postoperative nausea and vomiting (PONV) due to the slowing of gastric motility. Halothane can cause reduction of renal blood flow, and thus glomerular filtration rate, by up to 50% whereas the other agents have little or no effect on the renal system. Halothane can also cause significant hepatic dysfunction (Box 6).

Musculoskeletal

All volatile anaesthetic agents cause dose-dependent muscle relaxation and potentiation of neuromuscular blocking agents. Malignant hyperpyrexia can be triggered by all the volatile agents.

Interaction with carbon dioxide absorbers

Sevoflurane is absorbed and degraded by both soda lime and baralyme. When mixed with soda lime in experimental situations sevoflurane forms five toxic compounds (A, B, C, D and E). These have shown to cause renal, hepatic and cerebral injury in rats. In clinical situations, it is predominantly compound A (and to a lesser extent, compound B) that is produced and reaches the highest concentration during low flow anaesthesia (<2 $l.min^{-1}$ per minute). This is, however, not thought to be of any clinical concern.

Non-volatile inhalational agents

Due to their analgesic and anaesthetic properties, N_2O and xenon have also been administered alone or combination with the volatile anaesthetic agents (Table 3).

Nitrous oxide

Nitrous oxide is an inorganic gas commonly known as 'laughing gas'. Despite early knowledge of its analgesic and anaesthetic properties it was not introduced into mainstream medical/dental practice until the late 1800s. Nitrous oxide is manufactured commercially by heating ammonium nitrate to a temperature of 245–270°C. This results in the formation of several compounds including ammonia, nitric acid, nitrogen, nitric oxide and nitrogen dioxide. The gases are purified and separated using a number of compressing, drying and evaporation processes before the pure N_2O is stored in cylinders.

Mechanism of action: nitrous oxide is predominately a NMDA-receptor antagonist, with little or no effect at $GABA_A$ receptors. It is also known to have stimulatory effects on dopamine, α_1- and α_2-adrenergic and opioid receptors.

Halothane-associated hepatic dysfunction

Halothane is known to cause hepatic dysfunction in some individuals. There are two types of dysfunction that can occur:

1. Halothane-induced liver dysfunction

This is a mild, transient derangement in liver function tests and usually resolves spontaneously over a few days. It is thought to occur because of hepatic tissue necrosis secondary to the metabolism of halothane in the liver.

2. Halothane hepatitis

This is an extremely uncommon but severe adverse effect of halothane anaesthesia. It is more common after repeated exposure. It takes the form of jaundice and fulminating hepatic necrosis with a mortality of 30–70%. It is thought to occur because of an immune response to certain fluoroacetylated liver enzymes that are formed during halothane metabolism. As a result of concerns regarding halothane hepatitis, the UK Committee on Safety of Medicines made the following recommendations:

- a careful anaesthetic history should be taken to determine any previous exposure and reaction to halothane;
- repeated exposure to halothane within a period of three months should be avoided unless there are overriding clinical consequences; and
- a history of unexplained jaundice or pyrexia after previous exposure to halothane is an absolute contraindication to its future use in that patient.

Box 6

Properties of nitrous oxide and xenon

	Nitrous oxide	Xenon
Uses	1. Analgesic and antinociception 2. As an adjuvant/carrier gas for induction and maintenance of general anaesthesia	1. General anaesthetic agent with analgesic properties
Chemical	Inorganic gas	Noble gas Atomic number 54
Presentation and storage	'French-blue' cylinders (pressure 44 bar) Cylinders contain liquid N_2O with gaseous N_2O above (therefore gauge pressure does not reflect cylinder content). Volume of liquid in cylinder when full is determined the 'filling ratio' (0.75 in UK, 0.67 in hotter climates) Piped medical gas (pressure 4 bar) Sweet smelling, non-irritant colourless gas	Odourless, colourless, inert gas
Physical properties	Molecular weight 44 Boiling point -88°C SVP at 20°C 5200 kPa Critical temperature 36.5°C Critical pressure 72.6 bar Non-flammable but supports combustion MAC 1.05 (in air/oxygen) Blood:gas solubility coefficient 0.47 Oil:gas partition coefficient 3.2	MAC 0.63—0.7 (in air/oxygen) MAC_{aw}0.33 Boiling point -108°C Molecular weight 131.2 Blood:gas solubility coefficient 0.13—0.2 Oil:gas partition coefficient 1.9
Uptake and distribution	Due to the low blood:gas solubility coefficient, the rate of equilibration of alveolar N_2O with inspired concentrations is rapid	Due to a very low blood:gas solubility coefficient, the rate of equilibration of alveolar xenon with inspired concentrations is very rapid
Metabolism and excretion	Excreted unchanged through lungs Undergoes no metabolism	Excreted unchanged through lungs Undergoes no metabolism
Other	Concentration/second gas effect (see above) Greenhouse gas	No impact on the environment

Table 3

Inhalational anaesthetic agents, the environment and occupational exposure

Except for xenon, all inhalational anaesthetic agents in current clinical use are greenhouse gases. Desflurane has a 10-year 'lifetime' in the atmosphere, compared with 3.6 years for isoflurane and 1.2 years for sevoflurane. Using desflurane for 60 minutes has the same environmental impact as 235—470 miles of driving.[8]

There have also been concerns over the impact of occupational exposure to inhalational anaesthetic agents. Increased miscarriage rate in female anaesthetists has been reported in the literature and attributed to N_2O exposure. Studies to date, however, are sparse and inconclusive with respect to this.

There are environmental exposure threshold limits for the inhalational agents which differ from country to country. For example, the threshold for N_2O in the UK is 100 ppm compared with 50 ppm in the USA.[9]

In recent years, the development of improved scavenging and ventilation systems, increased attention to leak detection and equipment maintenance, and the increasing use of low-flow anaesthesia have all contributed a reduction in the environmental impact of inhalational agents.

Box 7

Systemic effects:

Cardiovascular effects — nitrous oxide is a direct myocardial depressant but in healthy patients this is rarely clinically significant as the effect is antagonized by sympathoadrenal stimulation and increased SVR. Pulmonary vascular resistance is increased and this may lead to increased right atrial pressure. For this reason, it is best avoided in patients with pulmonary hypertension.

Respiratory effects — similar to the volatile inhalational agents, N_2O causes a dose-dependent decrease in tidal volume with compensatory increase in respiratory rate. It also obtunds the ventilatory response to hypoxaemia and hypercapnia. It is non-irritant to the respiratory tract and is often used during gaseous induction.

Central nervous system effects — nitrous oxide causes an increase in cerebral blood flow, cerebral metabolism and intracranial pressure. These changes are more marked in patients with abnormal cerebral autoregulation. Prolonged, repeated exposure to N_2O may result in a myeloneuropathy similar to subacute combined degeneration of the spinal cord. This is caused by N_2O-induced oxidation of vitamin B12, which inhibits the activity of methionine synthase (see below).

Gastrointestinal – nitrous oxide has long been considered a significant risk factor in the development of PONV. This effect is likely to be multifactorial in origin secondary changes in middle ear pressures, bowel distension and activation of dopaminergic neurones.

Effect on enclosed gas spaces – nitrous oxide can diffuse out of blood into enclosed air spaces (e.g. bullae, pneumothoraces, inner ear, sinuses) faster than nitrogen can exit. For compliant gas-filled spaces such as the bowel lumen, the volume of the cavity may increase. However, in non-compliant spaces such as the inner ear, the pressure will increase. In both situations significant injury can result from increasing pressure and/or volume including tympanic perforation, bowel perforation, and an increase in the size of pneumothoraces. Nitrous oxide can also increase the size of air emboli in the blood and tissues; for this reason N_2O is avoided in cardiothoracic surgery and neurosurgery where air emboli are more common.

Other effects – nitrous oxide causes oxidation of the cobalt ion present in vitamin B12 which is required as a cofactor for methionine synthetase. This causes a reduction in DNA synthesis in leukocytes and erythrocytes and can result in megaloblastic anaemia if N_2O is delivered for more than six hours. Agranulocytosis can develop after prolonged (days) exposure. Teratogenic changes have been observed in pregnant rats exposed to N_2O. There is no evidence that this occurs in humans; however, N_2O is usually avoided in the first trimester of pregnancy.

Entonox: entonox is a 50:50 mixture of N_2O and oxygen and is used for analgesia during painful procedures. It is manufactured by bubbling oxygen though liquid N_2O. The two gases dissolve into each other creating a gas mixture that does not behave in a way that could be predicted from their individual properties (the 'Poynting effect'.)

Entonox is presented as a gas in French-blue cylinders with white and blue checked shoulders at a pressure of 137 bar when full. Below its pseudocritical temperature of -7°C, entonox can separate into its constituent parts due to liquefaction of N_2O. This can result in the delivery of a hypoxic mixture as the cylinder empties.

Xenon

Xenon is a colourless, dense and odourless gas in group 18 of the periodic table. It is found in the Earth's atmosphere in trace amounts and was the first of the noble gases to be discovered in 1951. It is used commercially for lasers, high-intensity flash lights/bulbs and as a propellant in jet engines.

Xenon, similar to N_2O and ketamine, acts by non-competitive inhibition of NMDA receptors in the CNS. Like N_2O, xenon has little or no effect on $GABA_A$ receptors.

Xenon would be a suitable alternative to N_2O as it is more potent and has a lower blood:gas partition coefficient (faster onset and recovery from anaesthesia). It also provides excellent analgesia, offers neuroprotective properties, causes little or no cardiovascular depression and has an unrivalled safety and efficacy profile.[7] Xenon is also the only inhalational anaesthetic agent that is not considered a 'greenhouse gas' (Box 7).

Xenon is manufactured using the fractional distillation of air. Unfortunately, due to its rarity it is very difficult (and therefore expensive) to manufacture, thus prohibiting its use in mainstream clinical practice at the present time. ◆

REFERENCES

1 The Royal College of Anaesthetists. Website. https://www.rcoa.ac.uk/college-heritage/the-history-of-anaesthesia.

2 S Khan K, Hayes I, Buggy D. Pharmacology of anaesthetic agents II: inhalation agents. *Cont Educ Anaesth Crit Care Pain* 2014; **14:** 106–11.

3 T.E Peck, S.A Hill, M Williams. Pharmacology for anaesthesia and intensive care medicine (4th Edition). Cambridge University Press.

4 White D. Editorial: uses of MAC. *Br J Anaesth* 2003; **91:** 168–9.

5 A.R Aitkenhead, I Moppett, J. Thompson. Smith and aitkenhead's textbook of anaesthesia (6th Edition). Elsevier.

6 Needham M, E Webb C, Bryden DC. Postoperative Cognitive Dysfunction and dementia: what we need to know and do. *Br J Anaesth* 2017; **119**(suppl 1)**:** i115–25.

7 D Sanders R, P Franks N, Xenon M Maze. No stranger to anaesthesia. *Br J Anaesth* 2003; **91:** 709–17.

8 M Molina Aragones J, Ayroa Ayora A, Barbara Ribalta A, et al. Occupational exposure to volatile anaesthetics: a systematic review. *Occup Med* 2016; **66:** 202–7.

9 Yasny JS, White J. Environmental implications of anaesthetic gases. *Anaesth Prog* 2012; **59:** 154–8.