# Pharmacology of anaesthetic agents II: inhalation anaesthetic agents

Revalidation
FOR ANAESTHETISTS
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**Key points**

Volatile anaesthetics exert their effects at multiple sites throughout the central nervous system.

It appears that volatile agents preferentially potentiate $GABA_A$ receptors and two-pore domain $K^+$ channels, whereas the anaesthetic gases nitrous oxide and xenon inhibit *N*-methyl-D-aspartate channels.

Uptake and removal of inhalation agents from the body depends on the alveolar concentration of the anaesthetic agent ($F_A$) and its uptake from the alveoli by the pulmonary circulation.

Xenon has many properties of the ideal inhalation anaesthetic but is currently prohibitively expensive to produce.

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The first reports of the use of inhalation anaesthetics such as ether (1846), chloroform (1847), and nitrous oxide (1844) began to emerge in the 1840s. Safety issues with early agents, especially chloroform, were quickly recognized and the search for better inhalation agents began with fluorinated ethers and hydrocarbons becoming the main focus of research and development. Since then halothane and enflurane have passed through common usage but have been largely replaced. The inhalation agents used in modern practice include the fluorinated ethers isoflurane, sevoflurane, and desflurane and the gas nitrous oxide ($N_2O$). The noble gas xenon has impressive anaesthetic properties, but production costs preclude its widespread use. These modern agents have greatly improved the safety, reliability, and applicability of general anaesthesia.

## Mechanisms of action of inhalation agents

This section on mechanisms of action of inhalation anaesthetics should be considered along with the section on mechanisms of action of i.v. anaesthetics in the accompanying review (Table 1).

By the 1870s, a wide range of structurally unrelated compounds were known to have anaesthetic properties leading Claude Bernard to postulate a common mechanism of action, the *'unitary theory of narcosis'*. Meyer and Overton observed a strong correlation between anaesthetic potency and solubility in olive oil, theorizing that anaesthetic agents act non-specifically on the hydrophobic, lipid components of cells. During the past few decades, however, it has been confirmed that actions on protein receptors (e.g. ligand gated ion channels) are responsible for many of the effects of inhaled anaesthetic agents. Potentiation at $GABA_A$ receptors by volatile anaesthetics and inhibition at *N*-methyl-D-aspartate (NMDA) receptors by the anaesthetic gases $N_2O$ and xenon are likely to be important mechanisms of action. Increasing experimental evidence on the role of two-pore domain potassium channels mediating the effects of inhalation anaesthetics has recently been reported.

The mechanisms of action of inhalation anaesthetics may be subclassified as macroscopic (brain and spinal cord), microscopic (synapses and axons), and molecular (pre- and post-synaptic membranes).[1]

### Macroscopic

At the spinal cord level, inhalation anaesthetics decrease transmission of noxious afferent information ascending from the spinal cord to the cerebral cortex via the thalamus, thereby decreasing supraspinal arousal. There is also inhibition of spinal efferent neuronal activity reducing movement response to pain.

Hypnosis and amnesia, on the other hand, are mediated at the supraspinal level. Inhalation agents globally depress cerebral blood flow and glucose metabolism. Tomographic assessment of regional uptake of glucose in anaesthetized volunteers indicates that the thalamus and midbrain reticular formations are more depressed than other regions. Electroencephalographic changes including generalized slowing, increased amplitude, and uncoupling of coherent anteroposterior and interhemispherical activity occur during anaesthetic-induced unconsciousness.[1,2]

### Synaptic

The actions of inhalation agents on ion channels of neuronal tissue can influence either the presynaptic release of neurotransmitters, alter the post-synaptic response threshold to neurotransmitters, or both. Inhaled anaesthetics are believed to inhibit excitatory presynaptic channel activity mediated by neuronal nicotinic, serotonergic,

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**Table 1** Factors affecting the uptake and release of inhalation anaesthetic agents

| |
|---|
| Alveolar concentration of inhalation agents |
| Inspired concentration |
| Fresh gas flow |
| Breathing system volume |
| Circuit absorption. |
| Alveolar ventilation |
| Functional residual capacity |
| Drug uptake from the lungs |
| Solubility (blood–gas partition coefficient) |
| Pulmonary alveolar blood flow (cardiac output) |
| Alveolar–venous partial pressure gradient |
| Second gas effect |

and glutaminergic receptors, while also augmenting the inhibitory post-synaptic channel activity mediated by $GABA_A$ and glycine receptors. The combined effect is to reduce neuronal and synaptic transmission.[3]

## Molecular

Recent evidence suggests that the interaction of general anaesthetics is dependent on precise molecular interactions with certain anaesthetic targets within the central nervous system (CNS). Effects of inhalation agents on α-subunits of the $GABA_A$ transmembrane receptor complex are likely to be important. GABA binding to its receptor leads to opening of a chloride channel leading to increased $Cl^-$ ion conductance and hyperpolarization of the cell membrane, thereby increasing the depolarization threshold. Inhalation anaesthetics prolong the $GABA_A$ receptor-mediated inhibitory $Cl^-$ current, thereby inhibiting post-synaptic neuronal excitability.[4,5]

Most recently, the role of two-pore domain potassium channels during inhalation anaesthesia has been described. Two-pore domain potassium channels are widely distributed in the mammalian central nervous system and are present both pre- and post-synaptically. Voltage independence coupled with absent activation and inactivation kinetics are characteristics of these channels. Conductances are referred to as leak or background conductances, and these set the resting membrane potential of a cell. Halothane, isoflurane, sevoflurane, and desflurane have been shown experimentally to enhance the activity of these channels, leading to hyperpolarization of the plasma membrane, thereby influencing the likelihood of neuronal action potential generation and potentially explaining their anaesthetic effects.[6]

# Pharmacokinetics of inhalation agents

The structure of the commonly used inhalation anaesthetics is shown in Figure 1. The clinical effect of inhalation anaesthetics is dependent on reaching therapeutic tissue concentrations in the CNS. Effect-site concentrations are related to the partial pressure of these agents in the CNS and are represented at equilibrium by the alveolar concentration. This process is dependent on a number of factors, which are summarized in Table 1.

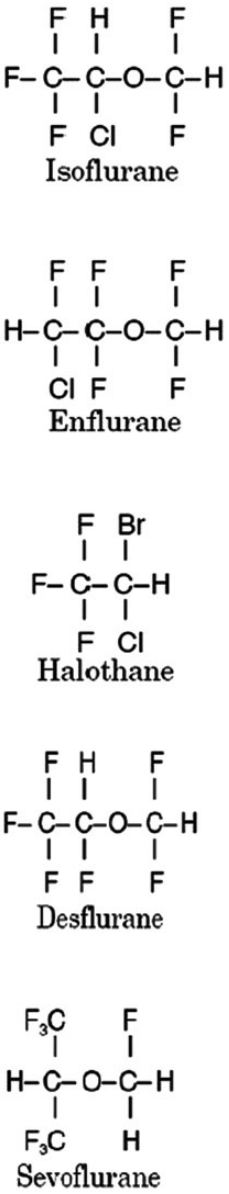


**Fig 1** Molecular structure of commonly used volatile anaesthetics.

In essence, the uptake and release of inhalation agents depends on the alveolar concentration of the anaesthetic agent and its uptake from the alveoli by the pulmonary circulation.

## Alveolar concentration of the inhalation agent

This, in turn, depends on three factors:

(i) Inspired concentration of agent: The concentration of inhaled anaesthetic affects the rate of increase of the alveolar concentration ($F_A$) towards the inspired concentration ($F_i$). The greater the inspired concentration, the more rapid the increase in the

$F_A/F_i$ ratio, and the faster the induction of anaesthesia. Higher fresh gas flow, lower breathing system volume, and lower circuit absorption leads to higher inspired gas concentration and faster induction and emergence from anaesthesia.

(ii) Alveolar ventilation: Increased alveolar ventilation results in faster increase in alveolar partial pressure by constantly replacing the inhalation agent taken up by the pulmonary blood flow.

(iii) Functional residual capacity (FRC): A larger FRC dilutes the inspired concentration of gas resulting initially in a lower alveolar partial pressure and therefore slower onset of anaesthesia.

## Drug uptake from the lungs

This, in turn, is influenced by four factors:

(i) Solubility (blood–gas partition coefficient)*:* A partition coefficient describes the relative affinity of an anaesthetic for two phases and hence how that anaesthetic partitions itself between the two phases when equilibrium has been achieved. The blood/gas partition coefficient reflects solubility of the volatile agent in blood and is defined as the ratio of its concentration in blood to alveolar gas when their partial pressures are in equilibrium. Isoflurane has a blood–gas partition coefficient of 1.4, meaning that at equilibrium, when there is no difference in the partial pressures between blood and alveolus, the concentration in blood is 1.4 times the concentration in the gas (alveolar) phase (Table 2). A higher blood–gas partition coefficient (higher solubility) leads to greater uptake by the pulmonary circulation, but a slower increase in alveolar partial pressure of the agent ($F_A/F_i$ ratio) and therefore more prolonged induction and recovery from anaesthesia. It is perhaps counterintuitive that anaesthetics with higher solubility in fact have slower onset and recovery, but the key factor determining the speed of onset and recovery from inhalation anaesthesia is the alveolar partial pressure of the agent, which is higher if the agent is less soluble in blood.

*Effect of plasma proteins and haemoglobin on blood–gas solubility.*

Blood–gas partition coefficients depend on the concentrations of serum constituents such as albumin, globulin, triglycerides, and cholesterol. These serum molecules effectively act as molecular sinks to bind anaesthetic agents, thereby increasing their blood solubility. The effects of haemocrit on solubility are variable. Increasing haematocrit leads to an increase in the solubility of enflurane but conversely to a decrease in the solubility of isoflurane. This discrepancy is explained by the relative affinities of the agents for red cells *vs* the serum constituents. Isoflurane has a weaker affinity for red cells than serum constituents with the opposite being true of enflurane.

(ii) Pulmonary alveolar blood flow (cardiac output): In the absence of a shunt, pulmonary blood flow equals cardiac output. Higher cardiac output results in a greater uptake of anaesthetic from the lungs and more rapid delivery to the tissues including the CNS. Enhanced delivery accelerates the equilibration of tissue anaesthetic partial pressures with that of arterial blood. However, this does not hasten induction, as the alveolar concentration is lowered by the high uptake of anaesthetic. In contrast, low cardiac output state results in slow uptake of anaesthetic agents and higher alveolar pressures (higher $F_A/F_i$ ratio), and therefore faster induction of anaesthesia.

(iii) Alveolar–venous partial pressure gradient and tissue uptake: The difference between alveolar and venous partial pressures is due to tissue uptake of inhalation agents. Tissue uptake is dependent on tissue blood flow, the blood to tissue partial pressure difference, and the blood tissue solubility coefficient. Brain tissue equilibrates quickly because it is highly perfused with blood. Lean tissue (muscle) has roughly the same affinity for anaesthetic agents as blood (blood tissue coefficient 1:1), but perfusion is much lower than brain tissue; therefore, equilibration is slower. Fat–blood coefficients are significantly $>1$. Such high affinity of fat tissue for anaesthetic and its low perfusion levels result in a very long equilibration time.

(iv) *Effect of obesity and age on blood–gas solubility and hence anaesthetic uptake*.

Obese patients have a larger fat compartment. This results in a longer time to equilibration after induction and a prolonged emergence time due to the high absorption and slow release of anaesthetic agents from fat tissue. Agents with lower fat tissue solubility such as sevoflurane, desflurane, and xenon reduce this effect.

The rate of induction is more rapid in infants and children than adults and corresponds to a more rapid increase in alveolar towards inspired anaesthetic partial pressure. This has been attributed to a larger ratio of alveolar ventilation to functional residual capacity, increased cardiac output, and greater delivery of cardiac output to vessel-rich tissues. Lower albumin and cholesterol levels in the young may also account for a reduction

**Table 2** Physical properties of inhalational agents. BP, boiling point; blood:gas, blood:gas partition coefficient; oil:gas, oil:gas partition coefficient; MAC, minimum alveolar concentration

| Characteristics | Isoflurane | Sevoflurane | Desflurane | $N_2O$ | Xenon |
|---|---|---|---|---|---|
| BP (°C) | 48 | 59 | 23 | −89 | −108 |
| Blood:gas (37°C) | 1.4 | 0.68 | 0.4 | 0.47 | 0.12 |
| Oil:gas (37°C) | 91 | 47 | 26 | 1.4 | 1.9 |
| MAC | 1.15 | 2.0 | 6.0 | 104 | 71 |
| Metabolism (%) | 0.2 | 5 | 0.02 | 0 | 0 |

in blood–gas solubility coefficients in these age groups and contribute to a more rapid onset of anaesthesia. Reduced albumin levels are also found in elderly adults and may account for the observed reduction in blood–gas solubility, similar to that in children. There appeared to be few age-related effects on blood–gas solubility of sevoflurane when neonates were compared with adults or when young adults were compared with elderly adults. The absence of an age effect may be due to low blood–gas solubility of sevoflurane.

The second gas effect: Although both nitrogen $N_2$ and $N_2O$ are relatively insoluble in blood, $N_2O$ is 30 times more soluble than $N_2$. Initial uptake of $N_2O$ from the alveolus is high, the associated loss of alveolar volume leads to concentration of and increases in the alveolar partial pressures of simultaneously administered agents (such as volatile anaesthetic agents) resulting in a higher $F_A/F_i$ ratio, leading to faster induction of anaesthesia. This effect also explains the phenomenon of diffusion hypoxia, which occurs during emergence from anaesthesia. When the inspired gas mixture is changed from $N_2O/O_2$ to $N_2/O_2$, the volume of $N_2O$ diffusing out from the mixed venous blood into the alveolus is greater than that of nitrogen taken up from the alveolus into the pulmonary capillary blood. Thus, the concentration of gases in the alveolus is diluted by $N_2O$, leading to a reduction in $P_{A_{O_2}}$. In healthy individuals, the risk of hypoxia is minimal but higher risk patients may require oxygen supplementation.

## Minimum alveolar concentration

The minimum alveolar concentration (MAC) is a measure of anaesthetic potency.

MAC is defined as the minimum alveolar concentration at steady state of inhaled anaesthetic at 1 atm pressure that prevents movement (e.g. withdrawal) in response to a standard surgical midline incision in 50% of a test population. It reflects the actions of an inhalation agent on spinal cord-mediated reflexes by measuring somatic responses and is not necessarily a surrogate for lack of awareness. The anaesthetic requirement for preventing consciousness is better estimated by the MAC-awake, that is, the end-tidal concentration of inhaled anaesthetics that prevents appropriate voluntary responses to spoken commands in 50% of a test population. This endpoint measures perceptive awareness rather than memory. MAC-awake is typically half the value of MAC but are more difficult to define as the endpoint of unconsciousness and are less clearly defined than movement. By performing anaesthetic washout experiments, it has been concluded that MAC awake is approximately one-third of MAC for isoflurane, sevoflurane, and desflurane.

## Pharmacodynamics of inhalation agents

### Effects on the respiratory system

All halogenated agents depress ventilation by reducing tidal volume. The concomitant increase in the respiratory rate does not compensate for the reduced alveolar ventilation, as it primarily results in increased dead-space ventilation. Consequently, $Pa_{CO_2}$ increases. All inhalation agents increase the threshold (i.e. decrease the sensitivity) of respiratory centres to $CO_2$. Isoflurane and sevoflurane decrease airway resistance, while desflurane does not produce any significant change in bronchial tone.

### Effects on cardiovascular system

All halogenated agents reduce mean arterial pressure and cardiac output in a dose-dependent manner. The reduction in mean arterial pressure by desflurane, sevoflurane, and isoflurane is primarily determined by the reduction in systemic vascular resistance. Sevoflurane may prolong the QT interval and should be administered with caution in patients with long QT interval syndrome. Overall, the arrhythmogenic potential of sevoflurane and desflurane is lower than that of isoflurane. Ischaemic preconditioning with inhalation anaesthetics may also reduce perioperative myocardial injury.

These effects are summarized in Table 3.[1]

### Effects on central nervous system

Inhalation agents modify electrical activity within the CNS as measured by EEG. Changes in average frequency and amplitude of the EEG show certain similarities with increasing doses of most inhalation anaesthetics. Low doses increase the power of the β-range, especially in the frontal regions, and decrease power in the α-range. Increasing anaesthetic dose to the level of surgical anaesthesia induces an average decrease in frequency towards the θ- and δ-range, with a corresponding increase in amplitude. With some inhalation anaesthetics (and also the i.v. anaesthetic propofol), higher concentrations will induce burst suppression. Volatile anaesthetics have been shown to initiate early ischaemic tolerance (preconditioning) in neurones, but models of focal brain ischaemia suggest it can take 24 h for preconditioning to develop fully.

Cerebral blood flow is autoregulated and coupled to cerebral metabolic rate in normal subjects. All inhalation agents decrease cerebral metabolic rate and oxygen consumption. They also partially uncouple the reactivity of cerebral blood flow to $CO_2$. The vasodilation of cerebral vessels caused by inhalation anaesthetics has the potential to increase intracranial pressure. It has been shown that neither desflurane nor isoflurane at one MAC concentration is

**Table 3** Cardiovascular effects of inhalational agents. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; HR, heart rate. ↔, no effect; ↓, decrease; ↑, increase; ↓↓, marked reduction

| Agents | CO | SVR | MAP | HR |
|---|---|---|---|---|
| Halothane | ↓ | ↔ | ↓ | ↓↓ |
| Enflurane | ↓↓ | ↓ | ↓↓ | ↑ |
| Isoflurane | ↓ | ↓ | ↓ | ↑ |
| Desflurane | ↔ | ↓ | ↓ | ↑ |
| Sevoflurane | ↔ | ↓ | ↓ | ↔ |
| Nitrous oxide | ↓ | ↑ | ↔ | ↑ |
| Xenon | ↔ | ↔ | ↔ | ↓ |

associated with a change in intracranial pressure in normocapnoeic patients. However, these agents reduce mean arterial pressure, resulting in decreased cerebral perfusion pressure.

### Effects on the liver

All inhaled anaesthetics reduce hepatic blood flow to some degree. Only 2–5% of current volatile anaesthetics isoflurane, sevoflurane, and desflurane are metabolized: they are mainly excreted unchanged in exhaled air.

Halothane undergoes ~25% metabolism by oxidative phosphorylation via hepatic cytochrome P450 systems. The major metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death. The National Halothane Study estimated the risk of fatal hepatic necrosis at one in 10 000 anaesthetics. Adult females are more commonly affected. Repeated exposure increases the risk of hepatitis. Less commonly hepatitis has been described after exposure to enflurane>isoflurane>desflurane and the risk of hepatitis correlates to the degree to which volatile agents undergo oxidative phosphorlation. Sevoflurane is not metabolized to antigenic TFA–protein complexes. Although there have been a few case reports of postoperative sevoflurane hepatic toxicity, the association is very weak.

### Effects on the kidneys

Older inhaled anaesthetics have differential effects on renal blood flow and glomerular filtration rate that are attenuated by renal autoregulation. Newer agents have minimal effects on physiology. The production of inorganic fluoride by the metabolism of halogenated agents may cause direct nephrotoxicity. Studies investigating methoxyflurane demonstrated an association between high fluoride levels (serum fluoride >50 μmol litre$^{-1}$) and polyuric renal failure. Serum fluoride levels peak earlier and decrease more rapidly with enflurane than with methoxyflurane, making enflurane less nephrotoxic. Isoflurane is more resistant to defluorination and can be used for prolonged periods without significant increases in serum fluoride levels. Sevoflurane undergoes significant defluorination and studies have shown that over half of the patients who had prolonged exposure had fluoride levels >50 μmol litre$^{-1}$. Despite the higher serum fluoride peak, evidence for a clinically meaningful effect of sevoflurane on renal function is currently lacking. Studies of sevoflurane use in those with pre-existing moderate renal impairment indicate that apart from higher serum fluoride levels, there were no differences in renal parameters measured. Halothane and desflurane are not significantly defluorinated.

#### *Compounds A and B*

The interaction of sevoflurane with carbon dioxide absorbents leads to the formation of several decomposition products. Trifluoromethyl vinyl ether known as Compound A is the major degradation product detected. Rodent experiments showed that when levels of Compound A reach 25–50 ppm or greater renal injury occurs. Human studies suggest a higher threshold for toxicity, explained by 20- to 30-fold lower levels of renal cysteine conjugate β-lyase enzymes, which converts Compound A into a reactive metabolite toxic to renal proteins. Total exposure expressed as the product of concentration by time correlates with injury. Human renal toxicity appears at ~150–300 ppm h. Prolonged exposure to sevoflurane, using a rebreathing system with a carbon dioxide absorber in lime, and low flows has been associated with transient biomarker evidence for renal injury, although urea and creatinine are unaffected. Significant clinical renal toxicity has not been associated with sevoflurane.

## Future trends

### Nitrous oxide: time for decommissioning?

$N_2O$ has been in clinical use for more than 150 yr. Concerns regarding the toxicity of $N_2O$, including hematological, neurological, immunological, and cardiovascular effects, and also postoperative nausea and vomiting and expansion of air-filled spaces, have been well documented. $N_2O$ neurotoxicity has been implicated in the development of cognitive defects when administered at either extremes of age, although definitive evidence is lacking.

$N_2O$ inhibits vitamin $B_{12}$, the co-factor required for activation of the enzyme methionine synthetase. Methionine synthetase is responsible for the conversion of homocysteine to methionine and the production of tetrahydrofolate. Inhibition of this enzyme results in elevated homocysteine levels, which is risk factor for cardiovascular disease. Reduced methionine synthetase activity may also lead to haematological complications such as megaloblastic anaemia and myelinopathies associated with subacute combined degeneration of the spinal cord. NMDA receptor antagonism may have specific toxicity in the developing nervous system.

More recently, the ENIGMA trial compared the use of oxygen in nitrogen ($F_{I_{O_2}}$ 0.8) *vs* oxygen in $N_2O$ ($F_{I_{O_2}}$ 0.3) by randomizing 2050 patients for major surgery. While duration of hospital stay was no different, a reduction in postoperative wound and respiratory tract infections, and severe postoperative nausea and vomiting was found in the non-nitrous oxide group. This trial was criticized because the design allowed different oxygen concentrations to be administered ($F_{I_{O_2}}$=0.3 or 0.8), to which the observed differences could be attributed.[7]

The same Australian lead group has now embarked on the ENIGMA II, enrolling 7000 patients with risk factors for coronary artery disease having non-cardiac surgery, to receive either an $N_2O$-free or an $N_2O$-containing maintenance anaesthetic mixture. Both groups will have the same fractional inspired oxygen concentration. The outcome measure will be a composite of death and major complications 30 days after surgery. This will ascertain the benefits (if any) of removing $N_2O$ from the anaesthetic gas mixture in surgical patients.[7]

## Xenon: the ideal anaesthetic?

Xenon is a noble gas present in minute quantities in the atmosphere and was first recognized as an anaesthetic in 1951. Argon and krypton also have anaesthetic properties but not under normobaric conditions. Although xenon's MAC is 71%, it may still be combined with safe levels of oxygen to deliver anaesthesia. Its blood:gas partition coefficient is 0.12, which results in an extremely rapid onset and recovery from anaesthesia. Xenon preferentially depresses postsynaptic excitatory transmission via NMDA receptor block. It has favourable clinical features, including minimal cardiovascular side-effects, even in the setting of severely limited myocardial reserve. Xenon affects anaesthetic-induced preconditioning of the heart and brain against ischaemic damage in the same way as the volatile agents do. Experimental models suggest that it has a significant neuroprotective action, but this benefit seems to be offset by an increase in cerebral blood flow, which elevates intracranial pressure. It is non-irritant to the airway, which favours smooth induction. Although a mild respiratory depressant, it decreases respiratory rate and increases tidal volume, in contrast to the volatile agents. Owing to its high relative density, xenon causes an increase in pulmonary resistance. Caution is advised in patients in whom an increased work of breathing may be deleterious, that is, severe chronic obstructive pulmonary disease and premature infants. It is not metabolized in the liver or kidneys and it does not trigger malignant hyperpyrexia. It is also a potent intraoperative analgesic, attenuating responses to surgical stimuli to a greater extent than sevoflurane. It is non-flammable and does not cause ozone depletion or environmental pollution. Xenon is manufactured from the liquefaction of air at a cost of approximately £10 litre$^{-1}$. Despite its many clinical advantages, these production costs have limited its widespread adoption in the UK.

## Declaration of interest

None declared.

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**Please see multiple choice questions 9–12.**