# Inhalational anaesthetics

Iain Moppett

**Abstract**

Inhalational anaesthetic agents include the halogenated organic compounds (halothane, enflurane, desflurane, isoflurane and sevoflurane), nitrous oxide and xenon. Their mechanism of action is becoming increasingly understood as well as the clinically important differences between agents. The use of xenon is relatively new and may assume greater importance in the future because of the environmental impact of the older agents.

**Keywords** Inhalation; nitrous oxide; side effects; volatiles; xenon

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## Learning objectives

After reading this article, you should be able to:

- explain the various mechanisms of action of inhalational anaesthetics
- describe the physical characteristics of commonly used inhalational anaesthetics
- compare the different physiological effects of commonly used inhalational anaesthetics
- discuss the adverse effects on patients and the environment of commonly used inhalational anaesthetics

## History

Inhalational anaesthetics have been used since the mid-19th century, when Long, Jackson, Morton and Wells first introduced nitrous oxide and ether. Since then various agents have come and gone, such as ether, chloroform, methoxyflurane and enflurane. Current agents in common use are nitrous oxide, halothane, isoflurane, sevoflurane and desflurane. Xenon is mainly used as an investigative drug, although it is in clinical use in Russia.

The halogenated compounds share many pharmacological and physical properties and tend to be considered as a group (the volatile agents). Nitrous oxide and xenon are rather less potent, with different pharmacological properties.

## Physical properties

The volatile agents are liquids at room temperature (Table 1), are poorly soluble in water and blood and have similar molecular weights. Each has a unique, pungent smell. Nitrous oxide and xenon are odourless gases at room temperature, and are also poorly soluble in water and blood.

## Mechanism of action

The exact mechanism of action of the inhaled anaesthetics is still unknown. Many theories have been suggested, the most pervasive being the Meyer–Overton lipid solubility theory. This theory hinges on two observations. First, the potency of many general anaesthetic agents correlates well (although not perfectly) with the solubility of the agents in olive oil. Second, the chemical structure of the general anaesthetic agents is quite diverse (Table 2). These observations led to the concept that these agents must be acting in some (unspecified) way at the neuronal lipid bilayer. Various explanations for this site of action have been given (membrane fluidity, lipid phase transitions, bilayer permeability). However, at relevant concentrations these explanations are biologically insignificant, and easily overwhelmed by normal physiological effects such as change in temperature. Furthermore, there is a degree of stereoselectivity of the agents, which is not explicable by physical effects. The demonstration by Franks and Lieb in the 1990s[1] of a correlation between anaesthetic potency and inhibition of the (protein) enzyme firefly luciferase, in the absence of any lipid, led workers to investigate membrane-bound receptors as targets for the action of general anaesthetics. Although evidence is still being sought, it is generally thought that the volatile agents facilitate the action of γ-aminobutyric acid type A and glycine receptor-mediated chloride conductance and the two-pore-domain potassium channels at the spinal and subcortical levels. Nitrous oxide and xenon probably affect n-methyl-D-aspartate receptors.

There are many methods of assessing anaesthetic potency. Classically, the minimum alveolar concentration (MAC) at near steady state that prevents movement in 50% of individuals in response to a standard surgical stimulus has been used. Increasingly, this is recognized as a spinal effect of anaesthesia, which may therefore not be directly related to the desired cerebral effects, such as hypnosis and amnesia. However, other MAC values may be more relevant in modern anaesthetic practice: $MAC_{awake}$ refers to the alveolar concentration of the agent at which the patient regains consciousness; and $MAC_{memory}$ refers to the concentration that prevents new memory formation. MAC can also be defined for other endpoints, such as cardiovascular or endocrine response to surgery ($MAC_{bar}$). Other modifications include $MAC_{95}$, which uses 95% of the population as its threshold. MAC is affected by various physiological and pharmacological factors. Neonates have a relatively low MAC, thereafter MAC increases up to about 1 year and then declines in an exponential fashion.[2] Some anaesthetic agent monitors display a MAC value for individuals aged 40 years, others produce an age-related figure. Nomograms and equations, based on meta-analyses of published data, are available to derive age-related MAC values. Co-administration of nitrous oxide lowers the MAC of volatile agents. When MAC (movement) is used, the effect appears to be additive: adding 0.1 MAC of nitrous oxide allows 0.1 MAC less of volatile. However, for $MAC_{awake}$ (0.64 MAC) and $MAC_{memory}$ (0.5 MAC) nitrous oxide is rather less potent than isoflurane (0.38 and 0.2 MAC, respectively). Therefore, simple addition of MAC values may overestimate the degree of anaesthesia. Opioids reduce MAC but there is a ceiling effect:

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**Physical characteristics of inhaled agents**

| Agent | Saturated vapor pressure at 20 °C (kPa) | Boiling point at atmospheric pressure (°C) | Blood–gas coefficient | Oil–water coefficient | MAC (%) | MAC with 70% nitrous oxide (%) |
|---|---|---|---|---|---|---|
| Halothane | 32.3 | 50.2 | 2.30 | 220.0 | 0.75 | 0.26 |
| Enflurane | 23.3 | 56.5 | 1.91 | 120.0 | 1.63 | 0.57 |
| Isoflurane | 33.2 | 48.5 | 1.40 | 170.0 | 1.15 | 0.41 |
| Sevoflurane | 23.5 | 58.5 | 0.60 | 55.0 | 1.7–2.0 | 0.62 |
| Desflurane | 88.5 | 23.5 | 0.42 | 18.7 | 5–10 | 2.30 |
| Nitrous oxide | 5500 | −88 | 0.47 | 3.0 | 104 | – |
| Xenon | Above critical temperature | −108.1 | 0.115 | 20.0 | 60–71 | – |

MAC, minimum alveolar concentration.

**Table 1**

regardless of the dose of opioid, about 0.3 MAC of volatile agent is required to prevent awareness.

Nitrous oxide and xenon are both analgesic at sub-anaesthetic concentrations, whereas the volatile agents are thought to either have no analgesic effect or attenuate the analgesic effect of nitrous oxide. Small studies in labouring pregnant women suggest that sevoflurane may be beneficial as a labour analgesic.

## Methods of administration

The volatile agents are administered by mixing fresh gas with gas containing volatile vapor. Provided the concentration of vapor from the vaporizing chamber is known and constant, then simple maths dictates the required ratio of fresh gas to volatile vapour-containing gas. To maintain the vapor concentration constant at saturated vapor pressure, the gas flowing through the vaporizing chamber is directed over a large surface area of the agent. Reduction in temperature due to latent heat of vaporization is minimized with heat sinks, and temperature compensation mechanisms adjust for changes in temperature. As a result, actual volatile concentrations leaving the vaporizer are relatively independent of fresh gas flow rates over the vaporizer range. Desflurane is administered slightly differently because of the close proximity of its boiling point to room temperature. The vaporizing chamber is heated to above boiling point so that the gas leaving the chamber is always 100% desflurane. New techniques involve direct injection of volatile vapor into the breathing circuit, which allows very precise and rapid control of inspired concentrations. Nitrous oxide is delivered from cylinders either on the anaesthetic machine or as part of the pipeline supply. Xenon is expensive, and so has specially designed closed delivery and recovery systems.

## Pharmacokinetics

Extensive research has given much information about the kinetics and distribution of the inhaled agents. Although current research uses state-of-the-art computational methods, the original descriptions by Mapleson, using water analogues, have largely stood the test of time. Many factors influence the speed at which the inhaled agents reach the required brain concentration. The concentration of agent in arterial blood is affected by: the pressure difference driving the agent across the alveolar membrane from alveolar gas into the blood; the length of time that a given volume of blood is in the pulmonary capillaries; the degree of ventilation–perfusion mismatch. The amount of agent that must dissolve in the blood to attain a given partial pressure is less for the less soluble agents, thus for a given inspired partial pressure, the arterial partial pressure rises more quickly.

Transport of the agent to the tissues is a function of relative blood flow and solubility of the agent in blood. The rate of rise of concentration in the tissues is a balance between supply and the capacity of the tissue. For organs with a good blood supply and limited capacity (e.g. the brain) rapid equilibration occurs. For less vascular tissues, with high capacity (e.g. fat) equilibration takes a long time to achieve, but the tissues may act as a long-acting depot for prolonged release of low concentrations of anaesthetic agent. The effect at the end organ (brain or spinal cord) is proportional to the partial pressure (not the blood concentration) of the agent. The observed effect of increased speed of induction with low cardiac output can thus be explained. Low cardiac output results in closer equilibration of arterial and alveolar concentrations, particularly for the more soluble agents. Cerebral blood flow is usually maintained at the expense of other organs and thus the delivery (flow multiplied by concentration) of agent to the brain increases. The speed of equilibration of inspired and arterial concentrations is usually attributed to the blood–gas solubility coefficients. However, despite essentially identical blood–gas solubility, nitrous oxide equilibrates faster than desflurane. This effect may be caused by differences in fat solubility, resulting in differences in inter-tissue equilibration rates.

**Second gas effect:** the relatively rapid absorption of nitrous oxide, compared with the volatile agents may be used to increase the rate of equilibration of the volatile agent. The removal of a significant volume of nitrous oxide from the alveolus results in a higher partial pressure of the co-administered volatile agent, and hence a higher driving pressure moving the volatile into the blood.

**Concentration effect:** high inspired concentrations of anaesthetic agents result in relatively fast induction and equilibration times. During the respiratory cycle a proportion of the anaesthetic agent