Anxiolytics, sedatives and hypnotics

Thimpe Beune
Anthony Absalom

Abstract
Anxiolytics and sedatives are used in current anaesthetic practice for two main reasons: for anxiolysis before surgery and as adjuvants during anaesthesia. A wide choice of agents are available. Their safety profile is dependent on their pharmacokineti c and pharmacodynamic profiles, patient comorbidity and the experience of the clinician using them. All sedative drugs have the potential to cause severe respiratory depression, and hence they should only be used with standard physiological cardiorespiratory monitoring. This is especially true of procedural sedation administered by non-anaesthetists in remote locations.

Drugs used for anaesthesia vary in their pharmacology, but have broadly similar clinical effects. The choice of drug is usually a matter of individual preference, although pharmacokinetic and pharmacodynamic parameters do influence the selection of anaesthetic agents, especially in day case surgery. Most intravenous agents are thought to alter consciousness by an effect at the voltage-gated ion channels.1 Most hypnotic anaesthetic agents are reversible agonists at the γ-aminobutyric acid type A (GABA\textsubscript{A}) or N-methyl-D-aspartate (NMDA) receptors or both. Our understanding of the mechanisms of action of anaesthetic drugs is incomplete, not least because of a lack of understanding of consciousness. Several theories have been proposed over the last century, but none of them has managed to comprehensively elucidate the processes involved. There is now a sense of expectation that understanding of anaesthetic agents on neurophysiology and their characteristics

After reading this article, you should be able to:

- discuss the influence of anaesthetic agents on neurophysiology and neural correlates of consciousness
- list the most important drugs used for anxiolysis and sedation and their characteristics
- list the most important drugs used for induction and maintenance of anaesthesia and their characteristics

Learning objectives

Influence of anaesthetic agents on neurophysiology and neural correlates of consciousness

One of the major theories of consciousness is the global neuronal workspace (GNW) hypothesis.\textsuperscript{2} Consciousness depends on global availability of information in the neuronal network and is defined by level and content. It is the result of a non-linear network ignition in the brain with recurrent processing which amplifies and sustains a neural representation that can be accessed by local processors.

The target sites of action of the anaesthetic agents are diverse, which has made the identification of a common mechanism of general anaesthesia challenging. Frontal parietal networks however, have been found to be metabolically affected by all major classes of general anaesthetics (propofol, sevoflurane and ketamine). In addition all agents except ketamine appear to reduce metabolism in the thalamus, either directly or indirectly. Functional disruption of the GNW may in part be caused by effects on the thalamus.

General anaesthesia is the result of the drug-induced disruption of information processing in the brain. The pharmacological action of the anaesthetic drugs overpowers the spontaneous dynamic activity that defines the functional connectivity between different areas of the brain. This disruption of the GNW reduces five sub-units. The diversity of these isoform sub-units enable considerable anatomical and functional diversity of the GABA\textsubscript{A} receptor, resulting in different spectra of effects with different agents. When activated, the receptor channel opens allowing an influx of chloride ions causing membrane hyperpolarization and inhibition of neural transmission.

In recent decades, much research has been focused on development of GABA\textsubscript{A} receptor subtype selective drugs, with the aim of finding drugs with more targeted physiologic effects as compared to currently available agents.

The N-methyl-D-aspartate (NMDA) receptor is a glutamate-gated cation channel. Ketamine, nitrous oxide and xenon are thought to act predominantly as NMDA receptor antagonists, thereby inhibiting excitatory neurotransmission. S-ketamine is more potent and associated with fewer adverse effects than R-ketamine, but the racemic mixture is the only formulation available in the UK.

The sedative and antinociceptive effects of clonidine and dexmedetomidine are mediated via an agonist effect on the presynaptic α2 receptors in the locus coeruleus, causing neuronal hyperpolarization and reduced norepinephrine release. The sedative effects are thought to be mediated by downstream effects on the natural sleep pathways.

Mechanisms of action of anxiolytics, sedatives and hypnotics

Molecular mechanisms
Growing evidence suggests that anaesthetic agents act by specific mechanisms on membrane proteins, especially ligand- and voltage-gated ion channels.\textsuperscript{1} Most hypnotic anaesthetic agents are reversible agonists at the γ-aminobutyric acid type A (GABA\textsubscript{A}) receptor, a G-protein coupled chloride channel with five sub-units. The diversity of these isoform sub-units enable considerable anatomical and functional diversity of the GABA\textsubscript{A} receptor, resulting in different spectra of effects with different agents. When activated, the receptor channel opens allowing an influx of chloride ions causing membrane hyperpolarization and inhibition of neural transmission.

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the probability that information is accessible to cognitive systems such as working memory.

Sedatives and hypnotics induce a dose-dependent spectrum of effects, including calmness, anxiolysis, drowsiness, and finally loss of consciousness. We have thus structured this review according to the indications for which the drugs are used.

**Drugs used for anxiolysis and sedation**

Anxiolytic and sedative medications are commonly prescribed preoperatively, albeit with declining frequency especially in day surgery settings (although there is no evidence that anxiolytic premedication delays discharge). The aim of premedication is to relieve anxiety in the preoperative phase and to reduce anesthetic requirements during induction, making anesthesia safer. Some patients, such as anxious children and adults, and adults with reduced mental capacity who constitute a risk to themselves or healthcare staff, may well benefit from preoperative sedation.

**Benzodiazepines** are the most commonly used agents for preoperative anxiolysis and sedation. The properties and dosages of some typical agents, as well as some newer agents, are summarized in Tables 1 and 2.

Benzodiazepines are potent anxiolytics, produce anterograde amnesia and have a favourable therapeutic index. They reduce induction dose requirements by several mechanisms including pharmacodynamic interactions with hypnotics. In most cases they are administered by the oral route, although the intranasal and rectal routes are also effective. Adverse effects include respiratory depression, impaired airway reflexes, cardiovascular depression, paradoxical reactions, and impaired consciousness and coma.

Benzodiazepines should be avoided or used with caution in the elderly or frail, in which both pharmacokinetic and pharmacodynamic factors may greatly enhance cardio-respiratory depression. Patients with impaired consciousness are also very sensitive to sedative agents. This is especially important in neurosurgical patients with space-occupying lesions, where any resulting respiratory depression is likely to cause or exacerbate raised intracranial pressure thereby amplifying the central nervous system depression and respiratory depression.

Remimazolam is a new ester-linked benzodiazepine, which is rapidly metabolized by tissue esterase to an inactive metabolite. It has been developed to permit fast onset, a short predictable duration of sedation, and a more rapid recovery than currently available benzodiazepines.

JM-1232 is an iso-indoline, and although it is not a member of the benzodiazepine group, it acts at the same binding site as the benzodiazepines. In animals, it has been shown to have favourable anaesthetic and sedative properties, with wide safety margins, and appears to have potential as an analgesic adjunct. Further human studies are needed.

**α-2 agonists:** when used in subsedative doses, dexmedetomidine and clonidine are useful premedicants in children and adults. Dexmedetomidine is sold as a formulation for intravenous use, but is sometimes administered intranasally. In addition to an intravenous formulation, clonidine is also available in tablet form.

**Other agents:** sedative doses of hyoscine are sometimes used for premedication, primarily for its anti-sialogogue effects.

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### Doses of agents commonly used for anxiolysis and sedation

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Intravenous (mg) (%/kg)</th>
<th>Adults Oral (mg)</th>
<th>Intramuscular (mg)</th>
<th>Oral (mg/kg)</th>
<th>Children Other (%/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>Healthy: 20–30</td>
<td>1 (elixir)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elderly, frail: 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>10–20</td>
<td>2.5–5 mg (iv)</td>
<td>100–150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.5–5</td>
<td>1–20</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Remimazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zopiclone</td>
<td>7.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>5–15</td>
<td></td>
<td></td>
<td></td>
<td>Oral transmucosal: ~10 μg/kg*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5–1.0 mg</td>
<td>0.2–0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyoscine</td>
<td>0.5–1.0 mg</td>
<td></td>
<td></td>
<td>50 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Chioral hydrate</td>
<td>Triclofos</td>
<td></td>
<td></td>
<td>50 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Dilazemetomidine</td>
<td>Continuous</td>
<td></td>
<td></td>
<td>0.5–1 μg/kg</td>
<td>Intransal</td>
</tr>
<tr>
<td>Melatonin</td>
<td>0.2–0.7 μg/kg/hour</td>
<td></td>
<td></td>
<td>1–1.5 μg/kg</td>
<td></td>
</tr>
<tr>
<td>MR04A3</td>
<td>0.075 mg/kg*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not licensed for sedation in the UK.

iv, intravenous; mcg, micrograms.

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Table 1

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Barbiturates are seldom used for premedication, because of their narrow therapeutic index, and the availability of safer agents. Opioids are occasionally used for premedication, particularly in those with pain and with cardiac disease, in whom the anxiolytic and sedative properties, and the attenuation of the stress responses to endotracheal intubation are particularly beneficial. In adults opioid premedication is often administered by the intramuscular route. In children oral transmucosal fentanyl citrate presented as a lolly produces reliable sedation. The disadvantage of using opioids for premedication is the common occurrence of adverse effects such as nausea and vomiting, blurred vision, pruritis and respiratory depression.

Other agents used for paediatric premedication include chloral hydrate (50 mg/kg po) and triclofos (50 mg/kg po). In uncooperative children intramuscular or rectal ketamine (2 mg/kg) just before an intervention may be useful.

Intravenous propofol, administered by a patient-maintained sedation system combining the benefits of patient control with target-controlled infusion technology, has been shown to be a safe and effective method of providing 'instant' anxiolysis and sedation during the preoperative period when respiratory and haemodynamic monitoring is present.

The neurohormone melatonin has anxiolytic and analgesic effects and can be used as an anaesthetic adjunct and premedication. Although experience with it is limited, it is registered for use in the UK and may have a future role in clinical practice.

Procedural sedation
Sedation during procedures such as endoscopy is commonly administered by the physician performing the procedure, or by a supervised non-physician. Mortality rates for these procedures are several orders of magnitude greater than for general anaesthesia. One factor likely to be responsible for this is the common practice of using drug combinations. Common combinations include intravenous bolus doses of fentanyl and midazolam, which have potent but variable synergism in terms of sedation and respiratory depression. Even when used alone, the pharmacokinetics of midazolam are sub-optimal, as the peak effect after an intravenous bolus dose only occurs at around 13 minutes, by which time many patients are already in the recovery area.

In the UK anaesthetists commonly administer sedation during surgical procedures performed under local or regional anaesthesia. Bolus doses of midazolam are often used, but have the disadvantage that repeat doses can be associated with prolonged sedation and recovery. Infusions of propofol offers several pharmacokinetic and dynamic benefits. These include potent anxiolysis, a rapid and pleasant onset of sedation, easy titration of sedation level, and a rapid clear-headed recovery. Target-controlled infusion (TCI) propofol is popular and has the benefits of ease-of-use, easy titration to clinical effect and stable blood concentrations. Patient-maintained propofol sedation may improve patient satisfaction, and has been shown to result in reduced propofol consumption and fewer adverse effects than anaesthetist administered propofol sedation.

Dexmedetomidine had been registered recently in the UK and has favourable properties for use during procedural sedation. It is a specific a2 agonist, with potency 8–16 times greater than clonidine. In addition to rapid kinetics, it produces analgesia and rousable sedation similar in some aspects to natural sleep. It is associated with less respiratory depression than other sedatives. Its properties of sedation, anxiolysis and analgesia together with its favourable pharmacokinetics make it a valuable adjunct for procedural and intensive care sedation. For light and moderate sedation in intensive care dexmedetomidine is associated with a shorter duration of mechanical ventilation and decreased incidence of delirium, when compared with benzodiazepines with no difference in duration of ICU or hospital stay.

Dexmedetomidine is increasingly being used for sedation and anxiolysis during specialized neurosurgical procedures such as deep brain electrode implantation, and awake craniotomies for excision of tumours where patient cooperation is required.

Hypnotics used for induction and maintenance of anaesthesia

Choice of agents
In adults, induction of anaesthesia is usually achieved by administration of intravenous anaesthetic agents. In infants and young children the inhalational route has traditionally been used, but in recent years the availability of topical local anaesthetic creams has resulted in increased popularity of intravenous induction. The availability of sevoflurane has meant that single breath or gradual inhalational induction of anaesthesia in adults is now not uncommon.

Anaesthesia is maintained by administration of a volatile anaesthetic agent or an intravenous agent. The advantage of volatile agents is the dependable pulmonary route of elimination versus the comparatively slow routes of elimination of some intravenous agents. The use of total intravenous anaesthesia for maintenance of anaesthesia is becoming more popular due to the availability of drugs with favourable pharmacokinetic profiles.

Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (oral) (%)</th>
<th>Vd (litres/kg)</th>
<th>t1/2 α (minutes)</th>
<th>t1/2 β (hours)</th>
<th>Clearance (ml/minute)</th>
<th>Active metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>80</td>
<td>1.3–1.5</td>
<td>48–162</td>
<td>5.1–15.3</td>
<td>60.9</td>
<td>No</td>
</tr>
<tr>
<td>Midazolam</td>
<td>48</td>
<td>0.8–1.14</td>
<td>3–38</td>
<td>2.1–2.4</td>
<td>202–324</td>
<td>No</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>93</td>
<td>1.14–1.3</td>
<td>3–10</td>
<td>14.3–14.6</td>
<td>77.0</td>
<td>No</td>
</tr>
<tr>
<td>Diazepam</td>
<td>100</td>
<td>0.9–1.2</td>
<td>9–130</td>
<td>31.3–46.6</td>
<td>26–35</td>
<td>Yes</td>
</tr>
<tr>
<td>Remimazolam</td>
<td>130</td>
<td>31.3</td>
<td>31.3</td>
<td>1213–1228</td>
<td>31.3</td>
<td>No</td>
</tr>
</tbody>
</table>

Vd, volume of distribution

Pharmacokinetic characteristics of benzodiazepines

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Dexmedetomidine is increasingly being used for sedation and anxiolysis during specialized neurosurgical procedures such as deep brain electrode implantation, and awake craniotomies for excision of tumours where patient cooperation is required.
and better delivery systems. The choice of individual agents, either intravenous or inhalational is dictated by personal preference as much as it is by clinical indications.

### Intravenous anaesthetics

The salient features of commonly used intravenous anaesthetics are summarized in Table 3.

**Propofol** is commonly used for induction of anaesthesia due to its favourable recovery profile. Its anti-emetic and anti-pruritic properties at subanaesthetic concentrations are particularly valuable in the day case setting. Propofol causes a significant reduction in arterial blood pressure by decreasing systemic vascular resistance, preload and myocardial contractility. These effects are more prominent in patients with compromised cardiac function and the elderly. An induction bolus dose of propofol commonly causes apnoea, as it inhibits hypoxic ventilatory drive, impairs the response to hypercarbia, and reduces upper airway reflexes. It also causes rapid reductions in intracranial and intraocular pressure, but will reduce cerebral perfusion pressure if the mean arterial pressure decreases significantly.

Pain during injection, bacterial contamination of preparations and unexplained excitatory phenomena remain important concerns with the use of propofol. Propofol injection pain is most effectively prevented by the use of a larger vein, such as the antecubital vein, or by pretreatment with lidocaine in conjunction with proximal venous occlusion. Some clinicians routinely avoid propofol in poorly controlled epileptic patients and those with a current driving licence, although it has been used as an adjunct in patients with status epilepticus. A rare but serious complication is the propofol infusion syndrome, associated with prolonged infusion (>48 hours) of higher doses (>4 mg/kg/hour) in children and young adults.

**Thiopentone** is the only barbiturate still in common use. It is mainly used for rapid sequence intubation or in patients who are allergic to propofol or its constituents. Nausea and vomiting, a prolonged recovery period and accumulation with repeated doses or infusions, are some of the factors responsible for its declining popularity. The organ system effects are generally similar to those caused by propofol. There is a higher incidence of laryngospasm and bronchospasm in lightly anaesthetized patients. Burst suppression signifying a reduction in cerebral metabolic rate usually follows large doses of thiopentone; these effects are considered to be protective in focal brain injury and might be of use in patients with status epilepticus.

**Etomidate** is most commonly used in emergency situations where propofol or thiopentone are likely to precipitate marked

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical group</th>
<th>Vd (litres)</th>
<th>Protein binding</th>
<th>t ½ α (min)</th>
<th>t ½ β (min)</th>
<th>Clearance (ml/kg/minute)</th>
<th>Metabolism</th>
<th>Induction dose (mg/kg)</th>
<th>Maintenance dose (infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>Phenol derivative</td>
<td>700–1500</td>
<td>97%</td>
<td>1.3–4.1</td>
<td>9.3–69.3</td>
<td>18–40</td>
<td>Hepatic and extra-hepatic. Inactive metabolites.</td>
<td>1.5–2.5</td>
<td>50–200 mcg/kg/min; TCI: 2–8 μg/ml</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>Barbiturate</td>
<td>130</td>
<td>80%</td>
<td>1.0</td>
<td>3.4–22</td>
<td>2.7–4.1</td>
<td>Hepatic oxidation to inactive metabolites</td>
<td>3–7</td>
<td>Not routinely used for maintenance</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Imidazole derivative</td>
<td>140–340</td>
<td>76%</td>
<td>1.2–4.5</td>
<td>1–4.7</td>
<td>12.5–26</td>
<td>Hydrolysis by plasma esterase and liver microsomal enzymes. Inactive metabolites</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>MOC etomidate</td>
<td>Etomidate derivative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Phencyclidine</td>
<td>210</td>
<td>20–50%</td>
<td>11</td>
<td>2.5</td>
<td>17</td>
<td>Norketamine-active metabolite Hepatic enzyme induction Hepatic extraction ratio 0.9</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Demetomidine</td>
<td>Selective α2 agonist</td>
<td>118</td>
<td>94%</td>
<td>6.2</td>
<td>2.0</td>
<td>39</td>
<td>none</td>
<td>0.2–0.7 mcg/kg 0.6–0.7 mcg/kg/hour</td>
<td></td>
</tr>
</tbody>
</table>

mcg, micrograms; MOC etomidate, methoxycarbonyl etomidate; TCI, target-controlled infusion; Vd, volume of distribution.

Table 3
hypotension. The classic example is rapid sequence intubation for emergency repair of an abdominal aortic aneurysm. Etomidate causes inhibition of 11β-hydroxylase and 17α-hydroxylase resulting in reversible adrenocortical suppression. As a result, continuous infusions of etomidate have been reported to increase morbidity and mortality in the critically ill. There is insufficient evidence, however, to extend this notion to its use for rapid sequence intubation as a single bolus.12

In an effort to solve the risks of adrenocortical suppression associated with prolonged infusions several etomidate analogues have been developed, most notably methoxycarbonyl (MOC) etomidate and cyclopropyl-methoxycarbonyl metomidate (CPMM). Although initial results from animal studies were promising, none have progressed beyond phase 1 human investigations.

**Ketamine** is a phencyclidine derivative that produces analgesia and a dissociative anaesthetic state. It has several beneficial effects including bronchodilation, relative preservation of airway reflexes and respiratory drive. Further it causes sympathomimetic effects, which can be beneficial for the cardiovascular system, but can be dangerous in patients with ischaemic heart disease. These pharmacodynamic effects are particularly beneficial in austere conditions, such as the battlefield or low resource settings. When used as a mono-anaesthetic it is associated with unpleasant postoperative psychomimetic effects including hallucinations and nightmares, which has limited its general use.

When used for maintenance of anaesthesia it can cause an increase in cerebral metabolic rate, blood flow and intracranial pressure. Ketamine is seldom used for patients requiring anaesthesia for neurosurgery. In the setting of traumatic brain injury, practitioners should weigh the benefit of better haemodynamic stability during induction of anaesthesia against the potential of increasing the intracranial pressure.

In the UK ketamine is more commonly used for sedation during regional techniques or awake fibroptic intubation, sedation of uncooperative patients (when it is sometimes administered intramuscularly), analgesia during change of burns dressings, and for postoperative pain relief in patients with chronic pain. It is also increasingly being used as an adjunct to other general anaesthetic techniques to reduce acute postoperative pain and opiate requirements.

**Inhalational anaesthetics**

The physicochemical properties of commonly used inhalational anaesthetic agents are summarized in Table 4. Among the volatile anaesthetic agents, potency, assessed by the MAC50 concentration, is generally proportional to the lipid solubility. Uptake of a volatile agent depends on the inspired concentration, alveolar minute ventilation, cardiac output and blood gas solubility. Rate of onset and offset of clinical effects depends on the concentration gradient from the alveoli to the pulmonary capillaries and the brain, and also on the blood—brain equilibration rate (determined by the lipid solubility). The alveolar-capillary concentration gradient is proportional to minute ventilation, and inversely proportional to cardiac output and blood-gas solubility co-efficient.

In the face of rapid climate change, sustainable healthcare is an important topic of discussion. The healthcare sector is a major contributor to the emission of greenhouse gases (GHG) worldwide, with anaesthesia and critical care contributing a significant proportion. In particular the production and use of inhalational anaesthetics plays a major role in the emission of GHG. Even with a fresh gas flow rate of 1 litre/minute, the GHG emissions of one MAC hour are equivalent to driving 6.5 km for sevoflurane, 13 km for isoflurane, and 300 km for desflurane. This knowledge has spurred a movement that advocates the decreased use of inhalational anaesthetics.15

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**Summary of important characteristics of volatile anaesthetic agents**

<table>
<thead>
<tr>
<th>PHYSICAL PROPERTIES</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>Halothane</th>
<th>Enflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Halogenated methyl ether</td>
<td>Halogenated ether</td>
<td>Halogenated ether</td>
<td>Halogenated hydrocarbon</td>
<td>Halogenated methyl ethyl ether</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>184.5</td>
<td>200</td>
<td>168</td>
<td>198</td>
<td>184.5</td>
</tr>
<tr>
<td>Boiling point (ºC)</td>
<td>48.5</td>
<td>58.5</td>
<td>23.5</td>
<td>50.2</td>
<td>56.5</td>
</tr>
<tr>
<td>SVP (kPa at 20ºC)</td>
<td>32</td>
<td>21.3</td>
<td>88.5</td>
<td>32</td>
<td>23.3</td>
</tr>
<tr>
<td>Oil gas solubility</td>
<td>174</td>
<td>53</td>
<td>18.7</td>
<td>220</td>
<td>120</td>
</tr>
<tr>
<td>Blood gas solubility</td>
<td>1.4</td>
<td>0.6</td>
<td>0.42</td>
<td>2.4</td>
<td>1.91</td>
</tr>
</tbody>
</table>

**SYSTEMIC EFFECTS**

<table>
<thead>
<tr>
<th>MAC (in air/70% N₂O)</th>
<th>1.15/0.50</th>
<th>0.2% (oxidation and dehalogenation)</th>
<th>1.7—2/0.7—2</th>
<th>5.7—10.6/1.7—7.7</th>
<th>0.75/0.29</th>
<th>1.68/0.57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excretion</td>
<td>0.2% in urine as non-volatile compounds; remainder exhaled unchanged</td>
<td>Exhaled predominantly unchanged</td>
<td>Traces of trifluoroacetic acid in urine; remainder exhaled unchanged</td>
<td>60—80% exhaled unchanged; urinary metabolites excreted for up to 3 weeks</td>
<td>2.4% (oxidation and dehalogenation)</td>
<td>2.4% in urine as non volatile compounds; 80% exhaled unchanged; high plasma fluoride concentrations;</td>
</tr>
</tbody>
</table>

Table 4

MAC, minimum alveolar concentration; SVP, saturated vapour pressure.
Nitrous oxide is the only commonly used non-volatile inhalational anaesthetic. It has a MAC50 of 105%, and thus cannot be used as a sole anaesthetic, but it does have unique advantages when used as a carrier gas. N₂O reduces the MAC and speeds up the onset of clinical effects of concomitantly administered volatile agents, has analgesic properties, and partially reverses the cardiorespiratory effects of volatile agents through its indirect sympathomimetic effects. These advantages are offset by the potential for adverse clinical effects including the expansion of closed air spaces, an increase in pulmonary vascular resistance, and postoperative nausea and vomiting. Prolonged exposure may result in megaloblastic anaemia and peripheral neuropathy by inhibition of vitamin B₁₂ dependent enzymes. It may also impair chemotactic responses and neutrophil motility, thus adversely affecting the immunological response to infection. Though the teratogenic effects of nitrous oxide have never been unequivocally proven, it is best avoided during the first and second trimesters of pregnancy.

Isoflurane is a volatile agent commonly used for maintenance of anaesthesia. It’s irritation of the airways makes it unsuitable for induction of anesthesia, but there is a theoretical concern of coronary steal in susceptible patients.

Sevoflurane: the physicochemical characteristics of sevoflurane (non-pungent, non-irritant to the airways and a low blood gas partition co-efficient) make it the agent of choice for inhalational induction of anaesthesia. Cardiovascular effects are minimal, and respiratory and cerebral effects are similar to those caused by isoflurane. Rapid emergence from anaesthesia is beneficial in the paediatric population. Concerns about compound A are now widely considered to be theoretical, although fresh gas flows greater than 2 l/minute are recommended.

Desflurane was initially developed and marketed for its rapid emergence even after prolonged anaesthesia. However, it has several unfavorable characteristics that are slowly pushing it into obsolescence. It is unsuitable for induction as it is a strong irritant to the airways and causes sympathetic activation especially with rapid onset of the alveolar concentration. Furthermore, it requires specifically designed heated vaporizers due to its low boiling point and has a significant environmental impact even when compared to other inhalational anaesthetics.¹⁴

REFERENCES
1 Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci 2008; 9: 370–86.