Pharmacology of anaesthetic agents: update and new insights

Donal J Buggy

Department of Anaesthesia, Mater Misericordiae University Hospital, University College Dublin & Eccles Unit, National Cancer Control Programme, Dublin, Ireland

Tuesday, 14 June 2011 8:30 - 9:15 Room: G105

This subject is obviously wide-ranging, with lectures justifiable for each individual agent used in common practice. Therefore, this lecture focuses on revision of the main pharmacodynamic and pharmacokinetic principles underpinning the most commonly used IV and inhalation anaesthetics in Europe, together with concise presentation of the evidence base in areas of active controversy and, finally, an outline of potentially exciting, emerging new anaesthetic agents.

What are the mechanisms of action of general anaesthetics?

Despite their introduction to clinical practice as long ago as 1846, the molecular mechanism of action of general anaesthetics remains elusive. To qualify as a putative site of action of general anaesthetics (GA), the candidate site or receptor must fulfil three conditions[1]:

• the GA agent must exert an effect (alter the function) of the receptor at clinically relevant concentrations;
• it must be present in the appropriate anatomic location to mediate the behavioural effects of the GA;
• stereoselectivity.

Estimates of free anaesthetic concentrations in the brain have now been obtained for propofol, with estimates based on anaesthetic concentrations in blood for less commonly used agents. Anatomic location can be considered in terms of the effects of GA agents:

• immobility: all GA agents depress spinal cord reflex pathways;
• amnesia: synaptic transmission in the hippocampus and amygdala is impaired by all GAs. These brain areas are associated with learning and memory;
• hypnosis: GAs have been implicated in the regulation of hypnotic action in the hypothalamus, the thalamus and the frontal cortex[2].

Stereoselectivity occurs when a molecule has a chiral carbon atom, that is, where isomers of the molecule are mirror images of each other based on that chiral carbon. Some stereoisomers have different general anaesthetic effects, for example, the [S][+] enantiomer of ketamine is a three-fold more potent anaesthetic than its [R][−] enantiomer.

General anaesthetics also have effects at both presynaptic and postsynaptic sites and on ion channels (both voltage-gated and particularly ligand-gated ion channels, including the GABA<sub>A</sub> and NMDA receptors)[3, 4]. For example, volatile agents’ mechanism of action is predominantly by prolonging chloride ion channel opening at inhibitory interneurons, by binding GABA<sub>A</sub> receptors, thereby facilitating postsynaptic inhibition[4]. In fact, the GABA<sub>A</sub> receptor fulfils all three criteria for a plausible target for anaesthetic agent action, being expressed in all CNS locations involved in hypnosis, amnesia, analgesia and immobility. It is the primary molecular target of the IV agents propofol and etomidate[5]. In contrast, the barbiturates, including thiopental, although active also at the GABA<sub>A</sub> receptor, seem to be less selective in their sites of action, with proven activity at kainite, AMPA and nicotinic cholinergic receptors[4]. Ketamine, on the other hand, produces anaesthesia by its action at the NMDA receptor and is inactive at GABA<sub>A</sub>[6].
Effects and pharmacokinetics of IV anaesthetics

Propofol (2,6-di-isopropylphenol), a lipophilic weak acid (pKa = 11) is very insoluble in water, so is formulated in an oil/water emulsion. This can be conducive to bacterial growth, but recent addition of the chelating agent EDTA has reduced this [7]. Although its volume of distribution is high, its clearance is even higher, greater than hepatic minute blood flow, suggesting an extrahepatic, as well as hepatic metabolism, to inactive compounds which are excreted by the kidney.

Thiopental and the anaesthetic barbiturates, are also water insoluble and are prepared in a carbonate salt to maintain an alkaline pH. Their fast onset is attributable to their rapid distribution to highly perfused tissues. The action of a single dose is terminated by distribution to muscle (vessel rich tissue), therefore its induction dose should be calculated based on lean muscle mass. Ultimate elimination of barbiturates is by hepatic metabolism and its clearance from plasma is slow. Furthermore, some metabolites of thiopental are active, further prolonging its effect [7].

Etomidate is rapidly redistributed after bolus injection and then undergoes ester hydrolysis in plasma and liver to inactive compounds. Its cardiovascular stability is attributable to reduced action on the sympathetic nervous system and baroreceptor reflexes compared with propofol and thiopental, rendering it suitable in patients with cardiovascular compromise [7].

Like the other main IV induction agents, ketamine is highly lipophilic, and is rapidly taken up into the CNS. It is cleared in the liver to norketamine, which is clinically active, but less so than its parent compound.

Midazolam is unique in that it is formulated as a water soluble pro-drug which undergoes pH dependent ring closure to form a lipophilic active form. It is rapidly cleared and metabolised in the liver to inactive compounds, in contrast to diazepam, which generates active metabolites.

Inhalation anaesthetics

The blood:gas partition co-efficient of inhalation anaesthetics (Table 1), which reflects their solubility in blood, determines their speed of onset and also the rate of recovery. Counter-intuitively, the more insoluble the anaesthetic (the lower the blood:gas partition co-efficient), the more rapid its onset. This is because poorly soluble agents in blood accumulate more rapidly in the alveoli, and hence alveolar partial pressure of the insoluble agents increases faster, facilitating induction [8].

<table>
<thead>
<tr>
<th>Property</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>N₂O</th>
<th>Xenon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point; °C</td>
<td>48</td>
<td>59</td>
<td>23</td>
<td>-89</td>
<td>-108</td>
</tr>
<tr>
<td>Blood:gas solubility</td>
<td>1.4</td>
<td>0.7</td>
<td>0.4</td>
<td>0.47</td>
<td>0.12</td>
</tr>
<tr>
<td>Oil:gas solubility</td>
<td>91</td>
<td>53</td>
<td>19</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>MAC</td>
<td>1.15</td>
<td>2.0</td>
<td>7.0</td>
<td>104</td>
<td>71</td>
</tr>
<tr>
<td>Metabolism (%)</td>
<td>0.2</td>
<td>5</td>
<td>0.02</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The oil:gas partition co-efficient correlates with their anaesthetic potency. Except for nitrous oxide (N₂O) and xenon, the gases are in liquid form at room temperature, and their saturated vapour pressure is about 0.3 of an atmosphere, which would be excessive for clinical use. Therefore, agent-specific, variable-bypass vapourisers are manufactured, which split the carrier gas (oxygen and air typically) into a fraction that passes in contact with the anaesthetic vapour and a majority fraction which bypasses the vapour. Evaporation of liquid anaesthetic into its vapour form cools the vapouriser and would reduce the anaesthetic content of the vapour, and the vapourisers are also temperature compensated. Because desflurane’s boiling point is at room temperature, its saturated vapour pressure (SVP) is high (about one atmosphere), so a special desflurane vapouriser is pressure compensated for changes in temperature and uses electrical current to induce evaporation.
The minimum alveolar concentration (MAC) is that concentration which inhibits gross purposeful movement to a surgical stimulus in 50% patients. It reflects the effect of the inhalation agent on spinal-mediated reflexes, but the anaesthetic requirement for preventing consciousness is better estimated by the MAC-awake, i.e. the level at which a motor response first occurs as anaesthetic concentrations decline. MAC-awake is typically half the value of MAC. Inhaled anaesthetics are almost entirely excreted unchanged, i.e. are not metabolised to any significant extent. Sevoflurane, which is broken down by soda lime to minuscule amounts of Compound A and is 5% metabolised to free fluoride and hexafluoroisopropanol, has been shown to be safe to the kidney, even in patients with clinical nephrotoxicity [9].

Nitrous oxide: time for decommissioning?

Despite being one of the first agents used in anaesthesia, the continued use of N₂O is currently shrouded in doubt following some recent insights gained from clinical evidence-based medicine. N₂O inhibits vitamin B₁₂, which in turn inactivates the enzyme methionine synthetase, thereby inhibiting folate metabolism and increasing homocysteine levels, which is a risk factor for cardiovascular disease. Long exposure could theoretically also cause megaloblastic anaemia and bone marrow failure. The ENIGMA trial enrolled over 2 000 patients for major surgery of at least 2 h duration to receive N₂O-free (FIO₂ = 0.8) or N₂O-based (FIO₂ = 0.3 and N₂O = 0.7) anaesthesia maintenance. The endpoints were duration of hospital stay and postoperative complications up to 30 days after surgery. Patients in the N₂O-free group had lower rates of major complications (OR = 0.71, 95% CI 0.56-0.89, p = 0.003) and nausea and vomiting (OR = 0.4, 95% CI 0.3-0.5, p = 0.001). Duration of hospital stay was similar, but N₂O-free patients were more likely to be discharged from intensive care than those receiving N₂O [10].

A follow up retrospective review of the patients enrolled in this trial by telephone, with survival, myocardial infarction (MI) and stroke as the end-points, found that N₂O did not increase the risk of death or stroke but did increase the risk of MI (OR = 1.59, 95% CI 1.01-2.51, p = 0.04) [11]. Based on these findings, the same Australian-lead group has embarked on the ENIGMA II trial, a 7 000 subject trial enrolling patients with risk factors for coronary heart disease having non-cardiac surgery. The outcome measure will be a composite of death and major complications 30 days after surgery [12]. This will ascertain the benefits (if any) of removing N₂O from anaesthetic gas mixtures in patients for major surgery.

Xenon: the ideal anaesthetic?

Xenon is a noble gas present in minute quantities (< 0.1 ppm) in the atmosphere. Although its MAC is 71%, it may still be combined with safe levels of oxygen to deliver anaesthesia. Its blood:gas partition coefficient is 0.12, rendering its onset and recovery extremely rapid. Its mechanism of action is at NMDA receptors. Xenon has minimal cardiovascular side-effects, even in the setting of severely limited myocardial reserve [13]. Moreover, although a mild respiratory depressant, it decreases respiratory rate and increases tidal volume, in contrast to volatile anaesthetics. Experimental models suggest it has a significant neuroprotective action, but this benefit seems to be offset by an increase in cerebral blood flow, in turn increasing intracranial pressure. It is also a potent intra-operative analgesic, attenuating responses to surgical stimuli to a greater extent than sevoflurane. The only obvious downside is its cost: xenon is manufactured from the liquefaction of air, at €15 per litre [8, 13].

Novel intravenous anaesthetics in development

New intravenous anaesthetic drugs are currently being developed because the existing agents, propofol, midazolam and etomidate have some limitations. Propofol harbours bacterial growth and can cause major cardiovascular depression, especially in compromised patients. Midazolam can also cause severe vasodilation and has a relatively slow onset to peak effect. Etomidate impairs the hypothalamus-pituitary-adrenal axis and results in adrenal suppression, possibly facilitating infective and septic complications [14].
Propofol derivatives

PFO713

Similar to propofol but has larger side chains at the 2,6 points on the phenol ring. It is also a GABA\(^\text{A}\) receptor agonist and produces reliable anaesthesia after bolus injection without pain and apparently with an improved cardiovascular side effect profile compared with propofol. However, its performance after continuous infusion remains to be evaluated [15].

Fospropofol

This is a phosphate pro-drug of propofol converted into propofol within 3 min after intravenous injection. Its onset and recovery is, therefore, slower. Whether it obtains a clinically useful role in future will depend on clinicians’ ability to learn use of a drug with delayed effects [14].

Etomidate derivatives

Methyl-carbonyl-etomidate (MOC-etomidate)

This rapidly metabolised analogue of etomidate causes transient (minutes) adrenocortical suppression. It appears highly cardiovascularly stable after single bolus injection in experimental animal models. Like the propofol derivates, however, its safety in continuous infusion remains to be evaluated [16].

Carboetomidate

This compound is without a nitrogen atom from the imidazole ring of etomidate, which greatly reduces its adrenocortical suppression while maintaining anaesthetic efficacy. It remains to be clinically tested for the troublesome etomidate side-effects of nausea and myoclonus [17].

Benzodiazepine analogue

CNS 7056

This is a new esterase metabolised benzodiazepine, with rapid onset, short duration and rapid recovery. It has been successfully used for sedation in upper GI endoscopy, and was well tolerated. This drug might reduce the risk of inadvertent over-sedation sometimes seen with midazolam [18].

Anaesthetic neurotoxicity

Recently, the assumption that anaesthesia-induced hypnosis is a reversible, drug-induced state has been challenged. Studies in animal models of the developing brain have shown that many anaesthetic drugs induce apoptosis (programmed cell death), and learning deficits when animals are exposed to them early in the postnatal period. The question is no longer whether lasting changes in the brain can occur from exposure to clinical anaesthesia, but whether they have any identifiable or preventive deleterious impact long term. More experimental and clinical research is warranted to fill our knowledge gaps about the neurocognitive consequences of routine clinical anaesthesia exposure [19]. Retrospective epidemiological studies currently in progress may soon help to define the impact of general anaesthetics on long-term cognitive function [20].
**Key learning points**

- Pharmacological criteria to be a candidate site for the action of general anaesthetics are: there must be effects at clinical concentrations; appropriate anatomical location; and appropriate stereoselectivity.
- The blood:gas partition co-efficient of an inhaled anaesthetic inversely reflects its speed of onset and recovery. The lower this co-efficient, the faster the onset and recovery.
- MAC-awake is the minimum alveolar concentration of anaesthetic gas at which first response occurs during emergence from anaesthesia. It is typically about half the traditional MAC value and reflects the MAC level necessary for hypnosis (unconsciousness).
- Avoiding nitrous oxide reduces major complications including myocardial infarction after prolonged major surgery. Further studies (ENIGMA II) are ongoing to elaborate this.
- Xenon, a noble gas, has many properties of the ideal anaesthetic, except that it currently seems prohibitively expensive to produce.
- There are a number of propofol, etomidate and benzodiazepine analogues in the early stages of new drug development but it is too early to tell if any will have a meaningful clinical impact.

**References**

6. Orser B, Pennefather BS, MacDonald JF. Multiple mechanisms of ketamine blockade at NMDA receptors. Anesthesiology 1997; 86: 903-17