Pharmacology of anaesthetic agents I: intravenous anaesthetic agents

Revalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 1A02

Khurram Saleem Khan FCAI FJFICMI
Ivan Hayes FCAI FJFICMANZ
Donal J Buggy MD MSc DME FRCPI FCAI FRCA

Key points

The precise mechanism of action of i.v. anaesthetics remains elusive, but most agents exert their action through potentiation of $GABA_A$ receptor activity.

Potentiation of $GABA_A$ receptors increases chloride ion conductance, resulting in inhibitory post-synaptic currents and ultimately inhibition of neuronal activity.

I.V. anaesthetic agents have wide-ranging effects not only in the central nervous system, but also in the cardiovascular, respiratory, and other major organ systems.

Newer i.v. anaesthetics are being developed, which are structurally related to propofol and etomidate. These novel agents may overcome some of the undesirable side-effects associated with their original counterparts.

Khurram Saleem Khan FCAI FJFICMI
Registrar in Anaesthesia
Mater Misericordiae University Hospital
Dublin, Ireland

Ivan Hayes FCAI FJFICMANZ
Consultant in Anaesthesia
Cork University Hospital
Cork, Ireland
Tel: +353 1 8032281
Fax: +353 1 8309563
E-mail: ivanhayes@yahoo.com
(for correspondence)

Donal J Buggy MD MSc DME FRCPI FCAI FRCA
Professor of Anaesthesia
Mater Misericordiae University Hospital
Dublin, Ireland

Outcomes Research Consortium
Cleveland, OH, USA

This review focuses on revision of key pharmacodynamic and pharmacokinetic principles underpinning the most commonly used i.v. anaesthetic agents and briefly outlines some newer i.v. agents, including propofol and etomidate analogues.

The introduction of thiopental into clinical practice in 1934 marked the advent of modern i.v. anaesthesia. Propofol and etomidate were developed more recently. Despite their excellent safety record, the ideal i.v. anaesthetic agent does not yet exist, because all of these agents produce undesirable cardiorespiratory depression. An ideal i.v. anaesthetic would induce hypnosis (unconsciousness), analgesia, and amnesia without any side-effects. Because no single i.v. anaesthetic is ideal, many drugs are used in combination to achieve the desired clinical effects.

Mechanisms of action

Historically, two ideas dominated thinking on the mechanism of action of general anaesthetics: the Meyer–Overton observation and the Unitary Hypothesis. Meyer–Overton independently reported that the potency of anaesthetic agents correlated with their lipid solubility, whereas the Unitary Hypothesis stated that while known general anaesthetics are chemically diverse agents, they produce their anaesthetic effects by a similar (unknown) mechanism. These ideas underpinned the doctrine that anaesthetics acted non-specifically on the lipid component of the neuronal cell wall. However, in 1984, Franks and Lieb demonstrated that most general anaesthetics inhibited the lipid-free enzyme firefly luciferase, indicating that they act directly with protein, that is, on specific receptor sites rather than with lipid membranes. Most present-day i.v. (and inhalation) anaesthetics have been shown to exert significant effects on ligand-gated ion channels, in particular $GABA_A$ receptors and also at other proteins responsible for neuronal activity, such as two-pore domain K^+ channels.[1]

Cutting edge mutagenic 'knock in' molecular techniques, whereby mutated native genes are introduced ('knock in') to experimental animals, avoids the problems of deleting receptor subunits, commonly associated with the 'knock out' mutation model. Knock-in models have shown that mutating the β3-subunit of the $GABA_A$ receptor reduces the sensitivity of mice to the i.v. anaesthetic etomidate, but not to inhaled anaesthetics. Conversely, evidence suggests that mice with genetic alterations in α-subunits of the $GABA_A$ receptor display differential anaesthetic sensitivity compared with 'normal' mice, suggesting that no single unifying target can explain the action of all modern general anaesthetics.[2]

However, modulation of $GABA_A$ receptors alone incompletely accounts for the mechanism of action of all anaesthetics. Clinical concentrations of N_2O and xenon, for example, deliver their effects through inhibition of *N*-methyl-D-aspartate (NMDA) receptors on excitatory glutaminergic neurones, suggesting further diversity of general anaesthetic action. Evidence is now emerging about a number of additional mechanisms of general anaesthesia, which may be summarized as follows:

1. Two-pore domain K^+ channels: These are a family of 15 K^+ ion channels defined by two P domains in tandem in their primary sequence, and characterized by voltage independence and absence of being inactivated by an action potential. These special K^+ channels are responsible for leak currents determining the resting membrane potential. Standard ATP-dependent K^+ channels are sequentially activated and inactivated by every action potential. They are widely distributed within the central nervous system and are modulated by most inhaled general anaesthetics. Ongoing research involving site-

doi:10.1093/bjaceaccp/mkt039 Advance Access publication 20 September, 2013
Continuing Education in Anaesthesia, Critical Care & Pain | Volume 14 Number 3 2014

directed mutagenesis has shown that these K^+ channels are present pre- and post-synaptically, and that some anaesthetic action is explained by pre-synaptic inhibition of excitatory neurotransmitter release, in addition to competitive inhibition at post-synaptic ion channel receptor sites.[3,4]

2. Extrasynaptic receptors: These include α5- and δ-subunit containing $GABA_A$ receptors, expressed mainly in the hippocampus, where their activation inhibits long-term potentiation and hence memory and learning. While these α5 receptors have been shown not to be involved in causing sedation or immobility, some extrasynaptic receptors are preferentially potentiated by i.v. anaesthetics.
3. Integrated neuronal network models of anaesthetic effect: Linking the effect of an anaesthetic at particular ion channel sites to its actual behavioural effects is fraught with difficulty. Much attention has focused on neural networks involved in sleep and arousal, including the ventrolateral preoptic area of the hypothalamus, the tuberomamilliary nucleus, and the ascending reticular activating system.[5]

Many i.v. anaesthetic agents mediate their effects by potentiating the activity of GABA (γ-aminobutyric acid) at inhibitory $GABA_A$ receptors. $GABA_A$ receptors are ligand-gated ion channels consisting of five subunits arranged around a central pore. There are a number of isoforms of the $GABA_A$ receptor, which determine its agonist affinity, probability of ion-channel opening, and conductance (and also location and expression on the post-synaptic membrane). There are six subtypes of α-subunits, three subtypes of β- and γ-subunits, and also δ-, ε-, and θ-subunits. The majority of $GABA_A$-gated ion channels include both α- and β-subunits, the most common combination in mammalian brain being a pentamer comprising two α-, two β-, and a **γ-**subunit ($\alpha_2\beta_2\gamma$). These pentameric $GABA_A$ complexes form chloride anion channels and are molecular targets for benzodiazepines, barbiturates, i.v. anaesthetics (propofol and etomidate), and volatile inhalation anaesthetics. Activation of the $GABA_A$ receptor leads to post-synaptic hyperpolarization of the cell membrane, inhibitory post-synaptic currents, and ultimately inhibition of neuronal activity.

A significant amount of the hypnotic action of propofol is mediated through binding to β-subunits of $GABA_A$ receptors. Through its actions on $GABA_A$ receptors in the hippocampus and prefrontal cortex, propofol inhibits acetylcholine release. This action appears to be important for the sedative effects of propofol. Propofol also induces inhibition of NMDA receptors that may contribute to its central effects. Etomidate was the first i.v. agent discovered to have $GABA_A$ subunit selectivity. It is very similar to propofol in its actions on $GABA_A$ receptors, but it appears that the β2- and β_3-subunits are more important for its hypnotic action.

Barbiturates bind to the $GABA_A$ receptor at the β-subunit. Like propofol and etomidate, this binding site is distinct from the binding site for GABA itself and distinct from the benzodiazepine binding site that is situated at the interface between the α- and γ-subunits of $GABA_A$ receptors.

Ketamine inhibits the excitatory neurotransmitter glutamate at NMDA receptors. It functions at the thalamus (which relays sensory impulses from reticular activating system to the cerebral cortex) and the limbic cortex (which is involved with the awareness of sensation).[6]

Pharmacokinetics of commonly used i.v. anaesthetic agents

Propofol

Pharmacokinetics

Propofol is a 2,6-diisopropylphenol and is a lipophillic weak acid (pK_a=11) (Table 1). It is very insoluble in water, so is formulated as 1% aqueous solution (10 mg ml^{-1}) in an oil-in-water emulsion containing soya bean oil, glycerol, and egg lecithin. This can be conducive to bacterial growth, but addition of the chelating agent disodium edetate has reduced this. Propofol can cause pain during injection which may be attenuated by co-administration of lidocaine or by formulation in medium chain, rather than long-chain triglycerides. It has a short initial distribution half-life (2–8 min). Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulphate, producing water-soluble compounds which are excreted mainly by the kidneys. Clearance of propofol is extremely high (greater than hepatic blood flow), suggesting additional extrahepatic, metabolism.

After single-bolus injection, blood propofol levels decrease rapidly as a result of redistribution and elimination. The initial distribution half-life is 2–8 min and elimination half-life is 4–7 h. The longer elimination half-life is indicative of distribution to fatty tissues with low perfusion, which results in a slow return of propofol to the central compartment. Because of this slow rate of return to the plasma compartment, propofol concentrations in the blood do not increase dramatically. The context-sensitive half-life for infusion of propofol lasting up to 8 h is <40 min. Therefore, emergence from propofol anaesthesia or sedation remains relatively rapid even after prolonged infusion.

Table 1 Pharmacokinetics of i.v. anaesthetic agents

	Propofol	Thiopental	Ketamine	Etomidate
Water-soluble	No	Yes	Yes	No
Half-life (initial) (min)	2	8.5	16	1
Half-life (terminal) (h)	4–7	12	3	5.4
Volume of distribution (litre kg^{-1})	4.6	2.4	3	5.4
Clearance (ml min^{-1} kg^{-1})	25	11	19	18
Protein binding (%)	98	80	12	75

Pharmacodynamic effects

The pharmacodynamic effects of a number of i.v. general anaesthetics on major organ systems are shown in Table 2.

Cardiovascular

Propofol reduces systemic vascular resistance, cardiac contractility, and preload. Patients with impaired ventricular function poorly tolerate significant reductions in cardiac output as a result of decreases in ventricular filling pressures and contractility. Heart rate increases secondary to activation of baroreceptor-mediated compensatory mechanisms in response to the reduction in cardiac output and systemic vascular resistance.

Respiratory

Like thiopental, propofol causes profound respiratory depression. A reduction in upper airway reflexes is helpful during intubation or laryngeal mask placements in the absence of paralysis induced by neuromuscular blocking agents.

Cerebral

Propofol decreases cerebral oxygen requirements, cerebral blood flow, and intracranial pressure. It also has useful antiemetic effects. Although during induction, it may cause spontaneous movements, muscle twitching, or hiccups, it has predominantly anticonvulsant properties at high infusion doses and causes burst suppression on EEG. It has been used successfully to terminate status epilepticus.

Potential toxicity

Long-term infusions of high doses of propofol cause 'propofol infusion syndrome' characterized by severe metabolic acidosis, rhabdomyolysis, renal failure, lipaemia, and cardiac failure in association with critical illness. There are now guidelines recommending maximum propofol infusion rates of 4.8 mg kg^{-1} h^{-1} for long-term sedation in intensive care patients.[6]

Thiopental

Pharmacokinetics

Thiopental is the most commonly used barbiturate and is derived from barbituric acid, a condensation product of urea and malonic acid. It is insoluble in water and is prepared in a carbonate salt to maintain an alkaline pH. Although it is highly protein-bound (80%), its high lipid solubility and high non-ionized fraction (60%) accounts for rapid brain uptake within 30 s. In patients with intravascular volume depletion, low serum albumin, or if the non-ionized fraction is increased (e.g. metabolic acidosis), higher concentrations within the brain and heart will be achieved for a given dose, increasing the risk of cardiovascular compromise. After a single bolus, thiopental is rapidly distributed to highly perfused, low volume tissue (e.g. brain and spinal cord) and is then more slowly redistributed to lean muscle tissue, which terminates the initial effect of the induction dose. The uptake of thiopental by adipose tissue is a minor contributor to termination of the effects of an induction dose, because of minimal perfusion to fatty tissue and thiopental's slow removal from it. However, after a continuous infusion, termination of thiopental's effects becomes increasingly dependent on these slower processes of uptake into adipose tissue and elimination by hepatic metabolism.

Pharmacodynamics

Cardiovascular

Thiopental causes direct myocardial depression, with decreased mean arterial pressure (MAP) due to inhibition of medullary vasomotor centre and reduced sympathetic outflow, resulting in dilatation of capacitance vessels. It results in an elevation in heart rate due to baroreceptor-mediated sympathetic reflex stimulation of the heart in response to decrease in cardiac output and arterial pressure. The effects are more pronounced in hypovolaemia, β-blockade, pericardial tamponade, and valvular heart disease.

Respiratory

Thiopental causes depression of the medullary ventilatory centre and decreases the response to hypercapnoea and hypoxia. It does not completely depress noxious airway reflexes and may predispose to laryngospasm and bronchospasm. It also has antanalgesic effects.

Cerebral

Thiopental decreases cerebral metabolic oxygen consumption rate ($CMRO_2$), the cerebral blood flow, and intracranial pressure. Large doses cause electrical silence (burst suppression) on EEG, which may protect the brain from episodes of focal ischaemia.

Table 2 Systemic effects of i.v. agents. SVR, systemic vascular resistance; MAP, mean arterial pressure; CBF, cerebral blood flow

Function	Propofol	Thiopental	Ketamine	Etomidate
Heart rate	Minimal effect	Increased	Increased	No effect
Contractility	Reduced	Reduced	Increased	No effect
SVR	Reduced	Reduced	Increased	Minimal effect
MAP	Reduced	Reduced	Increased	Minimal effect
Respiratory	Depression	Depression	Bronchodilation	Minimal effect
CBF	Decreased	Decreased	Increased	Decreased
Adrenal cortex	—	—	—	Functional inhibition

Potential toxicity

Owing to slow metabolism and prolonged elimination kinetics, thiopental is rarely used as a continuous infusion. No specific toxicity has been associated with it, other than extension of its known side-effects.

Etomidate

Etomidate is an imidazole derivative, first introduced into clinical practice in 1973. It is highly protein-bound, has a rapid onset of action due to its high lipid solubility and large non-ionized fraction at physiological pH. Redistribution is responsible for decreasing its plasma concentration. It undergoes rapid hydrolysis by plasma esterases and hepatic microsomal enzymes.

Pharmacodynamics

Cardiovascular

Etomidate is known for its cardiovascular stability in comparison with propofol and thiopental. At induction dose of 0.3 mg kg^{-1}, etomidate has no effect on systemic vascular resistance, myocardial contractility, and heart rate.

Respiratory

Etomidate has minimal effect on ventilation and does not cause apnoea at appropriate clinical doses.

Cerebral

Etomidate decreases cerebral metabolic rate, blood flow, and intracranial pressure to the same extent as thiopental. Because of minimal cardiovascular effects, cerebral perfusion pressure is well maintained.

Potential toxicity

Etomidate binds to the P450 enzyme 11-β-hydroxylase, which is important for steroidogenesis. This effect is due to binding of a nitrogen atom in etomidate's imidazole ring to the Fe^{2+} within the haem ring on the 11-β-hydroxylase enzyme resulting in the inhibition of steroid formation.

Long-term infusions of etomidate cause adrenocortical suppression. This led to abandonment of etomidate's use as a sedative in intensive care units. Recently, it has fallen out of favour as an induction agent for similar reasons, although the importance of adrenal suppression after a single bolus is unclear.

Ketamine

Ketamine, a phencyclidine derivative, was first introduced into clinical anaesthesia in 1966. Ketamine is more lipid-soluble and less protein-bound than thiopental and is ionized at physiological pH, resulting in rapid onset of action. Again, its immediate reversal is due to redistribution to the peripheral compartment. It is metabolized in the liver to norketamine which is clinically active but less so than its parent compound.

Pharmacodynamics

Cardiovascular

Ketamine, in contrast to other i.v. anaesthetics, increases arterial pressure, heart rate, and cardiac output due to central stimulation of the sympathetic nervous system. It increases the pulmonary arterial pressure and myocardial work. It is relatively contraindicated in patients with coronary artery disease and poorly controlled hypertension. It is often used as an i.v. anaesthetic agent in patients with acute hypovolaemic shock.

Respiratory

Ketamine has minimal effects on ventilatory drive. It is a potent bronchodilator and preserves upper airway reflexes, but patients with increased risk of aspiration may require airway protection.

Cerebral

Ketamine increases cerebral blood flow, intracranial pressure, and cerebral oxygen requirements. It induces a state of *dissociative anaesthesia* which results in the patient appearing conscious (e.g. eye opening, swallowing, muscle contraction) but unresponsive to pain. Unpleasant dreams, hallucinations, and delirium may follow its use, but these adverse effects can be minimized by co-administration with benzodiazepines. It has analgesic and opioid-sparing properties.

Potential toxicity

Numerous animal studies in rodents indicate that NMDA receptor antagonists, including ketamine, induce neurodegeneration in the developing brain. There is also evidence that other general anaesthetics, such as isoflurane, can induce neuronal cell death (apoptosis) in neonatal animal models during key neurodevelopmental periods, which may be exacerbated by concurrent administration of midazolam or nitrous oxide. Concern has recently arisen regarding the safety of anaesthesia in infants and children. There are insufficient human data to either support or refute the clinical applicability of these findings. Prospective randomized clinical trials are underway to address the clinical significance of these findings.[7]

Novel i.v. anaesthetic agents

Propofol derivatives

PF0713

This is similar to propofol but contains larger side chains at the 2, 6 positions on the phenol ring (Fig. 1). It contains two defined chiral centres and is also a potent $GABA_A$ receptor modulator producing reliable anaesthesia after bolus injection without pain and an improved cardiovascular side-effect profile compared with propofol. This molecule has a reduced aqueous phase concentration compared

with propofol, which may explain its lack of pain on injection. However, its performance after continuous infusion remains to be evaluated in clinical trials.

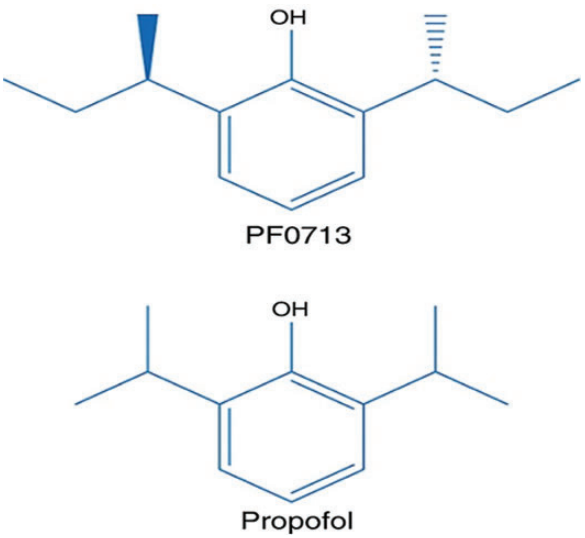

Fig 1 PF0713 is (*R*,*R*)-2,6-di-*sec*-butylphenol, a compound very similar to propofol. Both the two and the six groups on the phenol ring are optically active and it is the *R*,*R* form that has been evaluated in man.

Fospropofol

Fospropofol is a phosphate pro-drug for propofol which is converted to propofol within a few minutes after i.v. injection. Induction of anaesthesia is delayed and recovery is correspondingly slow. It does not cause pain on injection. However, it may cause perineal pain or paraesthesia. Whether it will be useful clinically will depend on its performance in comparative clinical trials and whether anaesthetists can determine how best to use this agent whose effect is delayed after administration.[8]

Etomidate derivatives

Methoxy-carbonyl-etomidate (MOC etomidate)

This rapidly metabolized analogue of etomidate causes only transient (min) adrenocortical suppression. It appears highly cardiovascularly stable after single-bolus injection in experimental animal models. Like the newer propofol derivatives, however, its safety in continuous infusion remains to be evaluated. MOC etomidate is less potent than the etomidate and propofol and given its brief duration of action, maintaining anaesthesia by infusion will require relatively large doses. However, adrenocortical suppression is likely for the duration of any infusion, potentially limiting its clinical applicability. It is rapidly metabolized to carboxylic acid and methanol. The safety of these metabolites is currently unclear (Fig. 2).

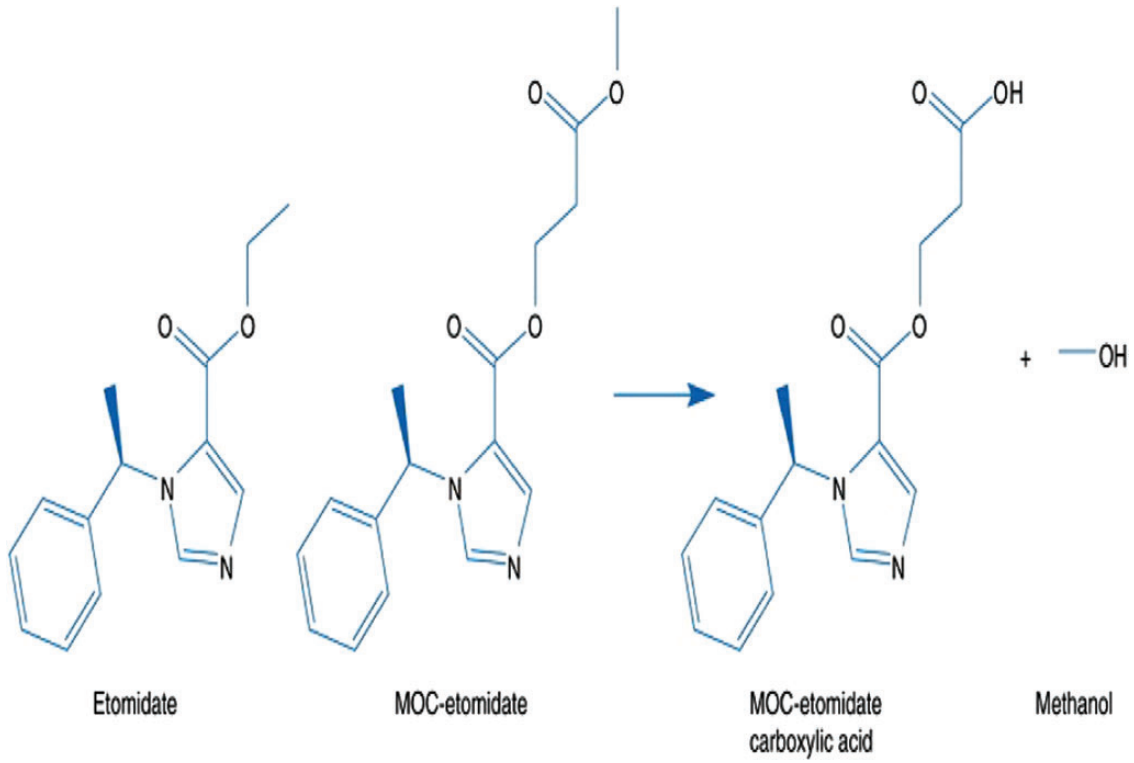

Fig 2 Etomidate, MOC-etomidate, and its inactive metabolite MOC-etomidate carboxylic acid.

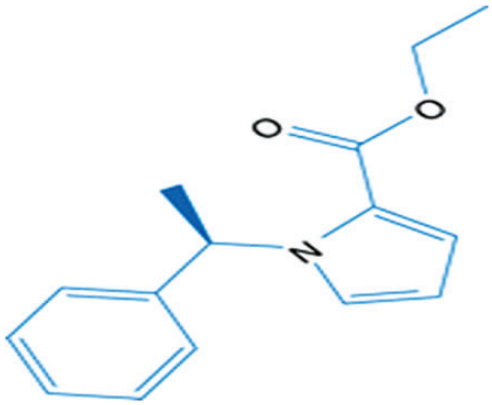

Fig. 3 Carboetomidate (note a nitrogen atom has been replaced within a carbon atom within the imidazole ring).

Carboetomidate

Carboetomidate is an etomidate analogue, with an alternative mechanism of minimizing adrenocortical suppression. Etomidate suppresses steroidogenesis by inhibiting the cytochrome P450 enzyme, 11 β-hydroxylase. Carboetomidate is modified in that it lacks a nitrogen atom within the imidazole ring of etomidate, which greatly reduces its ability to inhibit steroidogenesis, thereby minimizing adreno-cortical suppression (Fig. 3). It produced minimal changes in arterial pressure in experimental animals. It may prove suitable for maintenance of anaesthesia or sedation where cardiovascular stability is particularly indicated, but again requires investigation in comparative clinical trials.[8]

Declaration of interest

None declared.

References

1. Harrison NL. General anaesthetics: mechanisms of action. In: Hemmings HC, Hopkins PM, eds. *Foundations of Anesthesia*, 2nd Edn. Philadelphia: Mosby Elsevier, 2006; 287–94
2. Perouansky M, Hemmings HC. Intravenous anaesthetic agents. In: Hemmings HC, Hopkins PM, eds. *Foundations of Anesthesia*, 2nd Edn. Philadelphia: Mosby Elsevier, 2006; 295–310
3. Campagna J, Miller K, Forman S. Mechanisms of action of inhaled anesthetics. *N Engl J Med* 2003; **348**: 2110–24
4. Wang DS, Orser BA. Inhibition of memory and learning by general anaesthetics. *Can J Anaesth* 2011; **58**: 167–77
5. Rodolf U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. *Nat Rev Neurosci* 2004; **5**: 709–20
6. Jacobi J, Fraser GL, Cousin DB *et al.* Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adults. *Crit Care Med* 2002; **30**: 119–41
7. Hudson AE, Hemmings HC. Are anaesthetics toxic to the brain? *Br J Anaesth* 2011; **107**: 30–7
8. Sneyd JR, Rigby-Jones AE. New drugs and technologies, intravenous anaesthesia is on the move again. *Br J Anaesth* 2010; **105**: 246–54

Please see multiple choice questions 5–8.