

Intravenous anaesthetic agents

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Abstract

This article summarizes the properties of the drugs frequently used for intravenous induction of anaesthesia. The mechanism of general anaesthesia is still largely unknown, and so the physicochemical properties, metabolism and side effects of these drugs are more relevant to their use than the way that they cause unconsciousness. This article also highlights some historical aspects of anaesthesia and new developments in drug administration.

Keywords barbiturates; benzodiazepines; ketamine; target-controlled anaesthesia

Historically, anaesthesia was administered by inhalation (with agents such as ether or chloroform). However, as patients lost consciousness, they frequently passed through a stage of 'hyperexcitability' (with associated muscular movement, gagging, coughing, vomiting, tongue biting or laryngeal spasm). Guedel termed this phase of anaesthetic induction 'stage 2'. In the 1870s, chloral hydrate was probably the first intravenous agent used, but this route was not popular until the 1930s, with the use of barbiturates. The advantage of intravenous induction of anaesthesia is that it is very rapid, and the patient passes through stage 2 nearly instantaneously, with fewer attendant risks.

However, there are some general disadvantages to intravenous anaesthesia. First, because surgical anaesthesia is so rapidly attained, the ensuing collapse of upper airway tissues and apnoea is more rapid. For those patients in whom an airway may be difficult to obtain (whether by manual methods, or by airway devices or tracheal intubation), rapid intravenous induction poses a particular danger. Thus, intravenous induction should be undertaken with caution in those patients predicted to have a 'difficult airway'. Second, because anaesthetic agents have some cardiovascular side effects, adverse effects (e.g. hypotension or depression of cardiac function) will be more rapid and profound with an intravenous technique than with inhalation induction. This may be of relevance when inducing anaesthesia in patients with hypovolaemia or cardiovascular disease. Third, a large part

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of the administered dose of inhalational agents is removed from the body by simple exhalation. In contrast, intravenous agents undergo more extensive metabolism before excretion. Therefore, metabolic abnormalities (e.g. with certain drugs, or deranged plasma albumin concentrations or liver failure) may influence function. Finally, the use of an intravenous cannula for administration of intravenous anaesthesia may not be suitable for all patients (e.g. children may be uncooperative) and inhalational induction may be preferred.

The ideal intravenous anaesthetic agent

Table 1 summarizes most of the desirable properties of an intravenous anaesthetic agent. Note that all of these properties may be unachievable in a single agent, and some are contradictory (e.g. a rapidly-acting drug is likely to be lipid soluble and so is unlikely to be equally water soluble). The properties of the agents discussed below should be assessed against these ideal properties.

Propofol

Propofol (2,6-diisopropylphenol) (Figure 1a) is arguably the most frequently used intravenous induction agent in the Western world. It is presented as a white oil-in-water emulsion containing 1% (weight-by-volume; or more recently 2%) propofol in soya bean oil (10%), egg phosphatid (1.2%) and glycerol (2.25%). The solution has a pH of around 7.0 and is stable at room temperature and is not sensitive to light.

Properties of an ideal intravenous anaesthetic agent

Physical and chemical properties

- Chemically stable
- Water soluble
- Long shelf-life
- Compatible with other fluids and drugs
- Bacteriostatic

Pharmacology

- Painless on injection
- Thrombophlebitis rare
- Harmless if injected intra-arterially (or extravasated)
- Low incidence of adverse reactions
- Rapid induction of anaesthesia
- Good anti-emetic, analgesic and anticonvulsant
- 'Inert' cardiorespiratory effects
 - No respiratory depression
 - No bronchoconstriction
 - No myocardial depression
 - No vasoconstriction or -dilation
- Predictable (dose-related) recovery and short duration of action
- Inert metabolites
- No adverse effects on kidneys, liver, or metabolism
- No drug interactions
- No teratogenesis
- Safe during breast-feeding
- No 'emergence phenomena' or 'hangover effect'
- Rapid recovery
- Can be infused long term

Table 1

Intravenous anaesthetic agents

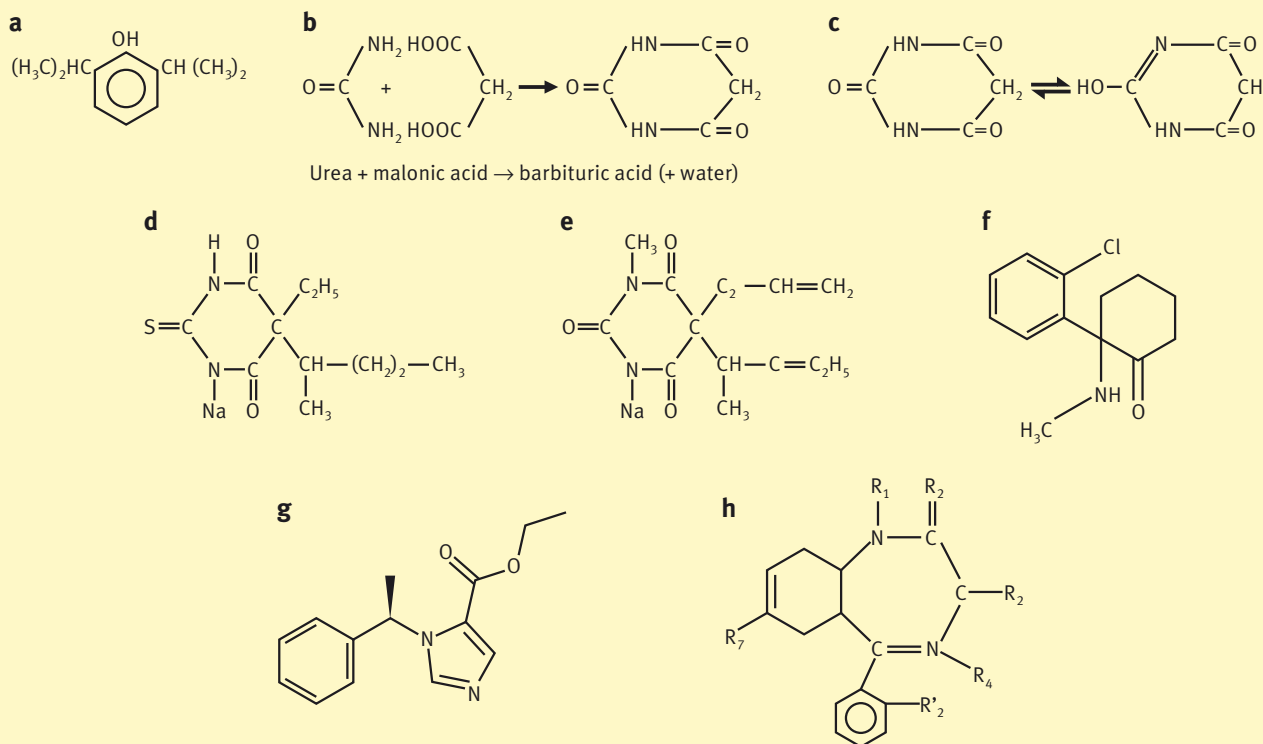


Figure 1 **a** propofol; **b** barbituric acid (2,4,6-trioxohexahydropyrimidine) formed by the condensation of malonic acid and urea; **c** keto–enol isomerization; **d** thiopental; **e** methohexital; **f** ketamine; **g** etomidate; **h** benzodiazepine structure.

The induction dose is around 1.5–2.0 mg/kg. Propofol is 98% protein bound and undergoes hepatic metabolism to glucuronide metabolites, which are ultimately excreted in urine.

Clinical effects: propofol produces rapid loss of consciousness, with a rapid, clear-headed recovery (as a result of its short distribution half-life and high clearance rate). Propofol depresses laryngeal reflexes making it particularly suitable for use with laryngeal mask airway devices, which can be inserted smoothly. There is a low incidence of postoperative nausea and vomiting and of allergic or hypersensitivity reactions. Since propofol does not significantly accumulate after repeat boluses, it is especially suitable for long-term infusions during surgery as part of a total intravenous anaesthesia (TIVA) technique and on the ICU for long-term sedation. Adverse effects of propofol include:

- pain on injection (which can be mitigated by addition of lidocaine (e.g. about 2 ml, 1% lidocaine to a bolus dose of 20 ml, 1% propofol))
- apnoea on induction
- hypotension (due to a combination of reduction in systemic vascular resistance and myocardial depression)
- excitatory side effects such as myoclonus.

Propofol is not licensed for use in children aged less than 3 years. There have been reports of unexpected deaths in children due to metabolic acidosis and myocardial failure after long-term use in the ICU.

Barbiturates

Barbituric acid (2,4,6-trioxohexahydropyrimidine), is formed by the condensation of malonic acid and urea (Figure 1b).

Barbiturates undergo keto–enol isomerization (Figure 1c); the keto form is favoured in alkaline solutions and substitution of the sodium ion (Na^+) for the hydrogen atom of the keto form results in water-soluble salts.

Barbituric acid lacks central depressant activity, but the presence of alkyl or aryl groups at position C5 (i.e. at CH_2 position in Figure 1b) confers sedative–hypnotic activity. The presence of a phenyl group at C5, or on one of the ring's nitrogen atoms confers anticonvulsant activity (e.g. phenobarbital). Long alkyl side chains at C5 increase hypnotic potency from five to six carbon atoms' length (above this, potency is reduced and convulsant properties may result). Compounds possessing the $\text{C}_2=\text{O}$ group are known as oxybarbiturates, and those having a $\text{C}_2=\text{S}$ group are known as thiobarbiturates. The thiobarbiturates generally have higher lipid solubilities than their corresponding oxybarbiturate.

Thiopental

Thiopental (Figure 1d) is presented as a sodium salt (0.5 g pale yellow powder) to promote dissolution of the drug in 20 ml water (to form a 2.5% solution). The powder also contains 30 mg anhydrous sodium carbonate, and the ampoule is filled with nitrogen (80 kPa; to prevent precipitation of insoluble free acid by atmospheric carbon dioxide). When prepared, the solution is not

stable and should be used within 24–48 hours, but can be kept up to a week in a refrigerator. The solution has a pH of 11–12 (i.e. strongly alkaline and bacteriostatic), and so is incompatible with many (basic) drugs, and is also very irritant on arterial injection or extravasation (both can lead to precipitation of non-ionized thiopental).

In common with most barbiturates, thiopental induces liver enzymes, increasing cytochrome P450 activity. After a single bolus dose, thiopental is rapidly redistributed in the body (to well-perfused organs such as brain, kidney and liver). A slower phase (about 1 hour) of uptake into muscle and skin then follows. Finally, there is a terminal decline in plasma concentration, which is due to slow metabolism (about 10%/hour) in the liver, where oxidation converts thiopental into inactive thiopental carboxylic acid. Plasma clearance is slow and almost entirely due to hepatic metabolism.

If large doses or infusions are used, metabolism becomes zero-order (i.e. independent of concentration) because of saturation of liver enzymes, and this accounts for delayed recovery. The combination of low clearance and large volume of distribution results in the relatively long elimination half-life (i.e. most of the drug is in tissues rather than plasma, and thus is not available for hepatic elimination). Therefore, thiopental is not amenable to TIVA techniques.

Clinical effects: the normal induction dose of thiopental is 3–5 mg/kg, and the effect is rapid. Thiopental is very lipid soluble and 80% is bound to albumin. Excitatory effects are rare, and, in contrast to propofol, loss of the eyelid reflex more reliably indicates unconsciousness.

Respiratory depression and apnoea occur after thiopental administration. Modest hypotension also occurs because of direct myocardial depression and venodilation (causing reduced venous return to the heart). The last two effects are pronounced in patients who are hypovolaemic or taking concurrent anti-hypertensive medication.

Thiopental has poor analgesic action. However, it has a particular potential beneficial action in its dose-dependent reduction of cerebral metabolic activity, which parallels the reduction in electroencephalogram activity. Stabilization of liposomal membranes, scavenging of free radicals and its anticonvulsant effects offer cerebral protection in injuries associated with raised intracranial pressure.

Thiopental induces histamine release (which can be associated with hypotension, bronchoconstriction and oedema). It can also precipitate acute intermittent porphyria.

Methohexital

Methohexital is an oxybarbiturate with a methyl group at the 1-N terminal (Figure 1e). It is a racemic mixture of two isomers, and is about three times more potent than thiopental. It is presented as a white powder mixed with 6% sodium carbonate to ensure stabilization, and is stable for up to 6 weeks after preparation. The prepared solution is 1% with a pH of about 10–11 (similar to thiopental). It is highly lipid soluble, 75% non-ionized at pH 7.4, and is 70–80% protein bound (i.e. has similar pharmacokinetics to thiopental).

Methohexital is eliminated almost entirely by the liver. The clearance is about three times higher than that of thiopental.

Therefore, after multiple doses, despite accumulation of methohexital in the peripheral tissues, recovery is more rapid than with thiopental.

Clinical effects: unlike thiopental, induction is frequently accompanied by transient twitching of skeletal musculature, hiccups and laryngospasm (about 45% of cases), the incidence being reduced with premedication. Therefore, methohexital should be avoided in patients with epilepsy because convulsions can be precipitated. However, this property makes it especially suitable for use in anaesthesia for electroconvulsive therapy in psychiatric practice.

Many of the other effects of methohexital on the cardio-respiratory system are similar to thiopental, but methohexital is less likely to cause bronchospasm in asthmatic patients and less cardiovascular depression than thiopental. Methohexital has relatively little effect on blood pressure.

Ketamine

Ketamine is an arylcyclohexylamine and structurally related to phencyclidine (Figure 1f). It has two isomers. The D-isomer is more potent than the L-isomer, but the parenteral solution is a racemic mixture. Ketamine hydrochloride is a white crystalline solid, which is soluble in water. It is supplied as 1, 5, and 10% solutions, which are stable at room temperature (benzethonium chloride is added as a preservative). The solution has a pH of about 3.5–5.5. Ketamine has a pK_a (acid dissociation constant) of about 7.5, with a lipid solubility of 5–10 times that of thiopental, but with a lower proportion of the drug binding to plasma protein (45–50%).

Termination of the anaesthetic action is due to redistribution, with early metabolism playing a lesser part. However, the clearance is rapid, resulting in the relatively short elimination half-life, which is due to both the high hepatic extraction ratio and the limited protein binding. Thus, clearance is sensitive to hepatic blood flow and agents such as halothane (which reduce hepatic blood flow) will decrease the clearance. The major pathway of hepatic metabolism is N-demethylation of the cyclohexylamine ring, forming norketamine, which is then hydroxylated to form hydroxy-norketamines, which may contribute to the undesirable side effects. Norketamine has about 20–30% of the activity of ketamine. These metabolites are subsequently conjugated and excreted in the urine.

Ketamine can also be administered intramuscularly but there is a delay of 20–25 minutes before adequate anaesthetic levels are reached.

Clinical effects: ketamine causes a ‘dissociative’ anaesthetic state; a functional/electrophysiological dissociation between the thalamocortical and limbic systems, characterized by catalepsy in which the eyes remain open with slow nystagmic gaze, while corneal and light reflexes remain intact. At subanaesthetic concentrations, ketamine produces good analgesia (unlike propofol or barbiturates). This may be related to its ability to suppress spinal cord activity via an effect on opioid κ receptors. However, nausea and vomiting are fairly common.

Ketamine induces psychotomimetic activity and emergence reactions (e.g. vivid dreams, hallucinations, and delirium). These can occur in up to 30% of patients and possibly in higher

proportions in those aged more than 16 years, females, patients with personality disorders, or with rapid intravenous injection. The incidence is not affected by covering the patient's eyes during emergence from anaesthesia or by allowing the patient to awaken in a quiet room. Adverse reactions may be lessened by preoperative discussion with the patient. Atropine and droperidol also may increase the incidence, while nitrous oxide supplementation decreases the dosage of ketamine and therefore the incidence of reactions. Benzodiazepines are probably the most effective drugs for attenuating psychic reactions.

The excitatory CNS effects of ketamine also include 'petit mal'-like seizure activity. There is an increase in cerebral metabolic rate, cerebral vasodilatation and a rise in systemic blood pressure. Thus, ketamine should be avoided in patients with potentially raised intracranial pressure.

As an intravenous induction agent, ketamine produces probably unique cardiovascular effects, with an increase in mean arterial blood pressure, heart rate, and pulmonary arterial and central venous pressures. All these effects are related to sympathetic stimulation, with increased circulating concentrations of catecholamines, resulting in peripheral vasoconstriction and direct cardiac stimulation. Therefore, the drug is a valuable induction agent for hypotensive or hypovolaemic patients, but these effects make it less desirable in those with ischaemic heart disease or raised pulmonary vascular pressures.

Respiratory depression is minimal and bronchodilatation occurs. These effects are potentially useful in patients with reactive airway disease. However, ketamine produces marked salivation, especially in children, therefore an antisialogogue should be administered before it is used.

Despite pharyngeal reflexes being preserved, and the upper airway remaining relatively patent with ketamine, airway management is still necessary, as with all intravenous induction agents. Laryngeal reflexes remain active (with the risk of laryngeal spasm) and regurgitation and aspiration are still possible. There is a transient rise in intraocular pressure, and eye movements and nystagmus may occur. Therefore, ketamine is best avoided for open eye injury.

Ketamine is potentially useful in children for short procedures as it may be given intramuscularly, orally or rectally (intramuscular doses for children are about 5–10 mg/kg with an onset of surgical anaesthesia in 3–5 minutes and a duration of 10–30 minutes). Ketamine is also a useful adjunct as a sedative to local and regional anaesthesia.

Etomidate

Etomidate is an imidazole derivative and exists as two isomers (only the (+) isomer is active) (Figure 1g). It is presented in 10 ml ampoules containing 2 mg/ml dissolved in water with 35% propylene glycol. The solution has a pH of about 8.1 and an osmolality of 4640 mosmole/litre. It is highly lipid soluble and protein binding is about 75%. Etomidate is therefore susceptible to factors that affect protein binding. The clearance rate is about six times that of thiopental. Etomidate is metabolized rapidly by hepatic enzymes and plasma esterases to an inactive carboxylic acid metabolite.

Clinical effects: the usual induction dose of etomidate is about 0.3 mg/kg. It has no intrinsic analgesic activity. Etomidate

decreases cerebral metabolic activity, cerebral blood flow and intracranial pressure. However, the agent has been associated with 'grand mal' seizures and increases epileptogenic activity in patients with seizure foci. There is frequent myotonic activity during induction, but this activity is not related to epileptiform discharges and may be decreased by opioid or benzodiazepine premedication. The incidence of nausea and vomiting seems to be more common with etomidate than with other intravenous agents.

Etomidate has minimal effects in healthy patients and those with cardiac disease, which makes the agent suitable for patients with hypotension, hypovolaemia or cardiovascular disorders (without the sympathomimetic actions of ketamine). Like propofol, there is a high incidence of pain at the site of injection (25–50%). It does not induce histamine release or increase bronchial reactivity.

Etomidate results in inhibition of adrenal corticoid synthesis by a concentration-dependent, reversible block of 11- β -hydroxylase. This occurs particularly when used as an infusion in the ICU.

Other agents and techniques of intravenous anaesthesia

Benzodiazepines are rarely used for intravenous induction of anaesthesia as sole agents, but are often used for premedication, as adjuncts to induction, or for sedation. The term benzodiazepine refers to the portion of the structure composed of a benzene ring, fused to a seven-member diazepine ring (Figure 1h). Because the important members of the benzodiazepine group contain a 5-aryl substituent and a 1,4-diazepine ring, the term has come to refer to the 5-aryl-1,4-benzodiazepines. The 5-aryl ring greatly enhances potency. Diazepam, lorazepam and midazolam are of particular interest. Diazepam and lorazepam have quite similar structures, while midazolam contains an imidazole ring bridging R1 and R2. Both diazepam and lorazepam are insoluble in water, and therefore require solubilizing agents, while the imidazole ring renders midazolam water soluble.

Benzodiazepines have high lipid:water partition coefficients in the non-ionized form. They are essentially completely absorbed after oral administration (with the exception of clozapate, which is converted to nordiazepam in the stomach before being absorbed) and the time to peak plasma concentrations varies from 0.5 to 8.0 hours. With the exception of lorazepam, most benzodiazepines are absorbed erratically after intramuscular injection.

The benzodiazepines are lipid soluble and protein bound, and redistribution is the major determinant of the onset and duration of effect after a single intravenous dose. Diazepam and the other highly lipid-soluble agents undergo enterohepatic circulation.

The duration of action varies from 2–5 hours (midazolam, triazolam) to 6–24 hours (lorazepam, temazepam, oxazepam, lormetazepam) and 24–48 hours (diazepam, nitrazepam, clorazepate). The longer-acting agents are metabolized in the liver by microsomal mixed-function oxygenase enzyme systems. Thus, cimetidine prolongs the effect of these agents, but ranitidine has no effect on the metabolism of benzodiazepines. Many of the metabolites (e.g. desmethyldiazepam) of benzodiazepines are pharmacologically active, contributing to the clinical effect of the drugs and extending the effective half-life. Intermediate- and short-acting agents are inactivated by glucuronidation and then eliminated by renal excretion. Therefore, for elderly patients and

those with hepatic disease, the intermediate- and short-acting agents are preferable.

The mechanism of action of benzodiazepines may be due to potentiation of the neural inhibition mediated by γ -aminobutyric acid (GABA), increasing chloride conductance via the GABA channel. The binding of the benzodiazepines to the GABA receptor is of high affinity, saturable and stereospecific. The ascending order of receptor affinity is diazepam, midazolam and lorazepam. Different degrees of receptor occupancy are thought to result in different clinical effects (e.g. anxiolysis with about 20% occupancy, sedation about 20–50%, and unconsciousness about 60%).

Diazepam is insoluble in water, and is therefore prepared commercially in an organic solvent, each millilitre of solution containing diazepam, 5 mg, propylene glycol, 0.4 ml, ethyl alcohol, 0.1 ml, benzyl alcohol, 0.015 ml, and sodium benzoic acid to a pH of 6.2–6.9. Diazepam is also available as an intralipid/water emulsion (*Diazemuls*). The clearance of diazepam is dependent on phase I hepatic metabolism, being oxidized and reduced to form active metabolites (desmethyldiazepam to N-desmethylation; ring hydroxylation to 3-hydroxydiazepam and oxazepam). These then undergo phase II reactions with conjugation to form inactive water-soluble glucuronides.

Midazolam is water soluble, and displays pH-dependent opening of the benzodiazepine ring below a pH of about 4.0. Thus, at physiological pH the ring is closed and lipid solubility is increased. It can also be administered intramuscularly or orally (the latter route is useful in sedating children before induction of anaesthesia). Midazolam is more protein bound than diazepam, and because of its imidazole ring has a higher hepatic metabolism. Metabolism occurs by oxidation, conjugation to water-soluble glucuronides and then excretion by the kidneys.

Clinical effects – these drugs do not cause true general anaesthesia, since awareness usually persists and relaxation sufficient for surgery cannot be achieved. However, they do cause anterograde amnesia (following injection), which makes them suitable premedicants and co-induction agents.

They have anticonvulsant activity and are used in the acute management of status epilepticus (diazepam), but tolerance develops and limits their usefulness in the long-term management of epilepsy.

Benzodiazepines generally have no analgesic properties but they seem to potentiate the effects of both narcotics and anaesthetics. They depress respiration and the responses to hypoxia and carbon dioxide but less so than other induction agents, and have minimal cardiovascular depressant effects. Thus, using them in addition to propofol or thiopental during induction enables the practitioner to reduce the doses of these two agents, thus minimizing cardiorespiratory depression.

Interactions with ethanol may be serious. Psychotic ideation rarely occurs but is more common in mentally ill patients. Rebound anxiety, ‘withdrawal type’ syndromes occur after cessation of prolonged therapy, and rebound insomnia also may occur after cessation. With chronic use they may lead to abuse and co-dependence.

The effects of benzodiazepines can be reversed with the specific antagonist flumazenil. Flumazenil is structurally similar to midazolam. The long-term use of benzodiazepines must be considered with caution because there may be withdrawal symptoms.

Agents of historical or research interest

Eugenols are the main constituent of oil of cloves, thus are insoluble in water. Propanadid was initially solubilized in *Cremophor EL* and since withdrawn from the market due to hypersensitivity reactions to *Cremophor*.

Steroids were not popular because of a high incidence of thrombophlebitis. Althesin, a mixture of alphaxolone and alphadolone in *Cremophor EL*, provided a rapid onset and rapid recovery; however, it also had a high incidence of hypersensitivity reactions and was withdrawn from the market. Minaxolone produced a rapid onset with a somewhat slower recovery than althesin, but toxicity in rats in some studies led to its withdrawal from clinical use. However, alphaxolone continues to be studied as a potential agent for use in clinical practice.

Droperidol is a butyrophenone, a fluorinated derivative of the phenothiazines (e.g. chlorpromazine, haloperidol). It is a potent anti-emetic with few respiratory or cardiovascular effects. However, it produces extrapyramidal side effects and was withdrawn from use over its possible triggering of a ‘neuroleptic malignant syndrome’ (a dramatic cardiovascular collapse with some features similar to malignant hyperthermia).

Dexmedetomidine is an α_2 -adrenoreceptor agonist with sedative and analgesic properties. It cannot be used as a bolus for induction, but can be used via infusion (for up to 24 hours). Its antisympathetic effects offer some cardiovascular stability and it can be used as an adjunct to other anaesthetics.

Neuroleptanaesthesia

With neuroleptanaesthesia, the idea is to produce a state of indifference to pain using any combination of agents with good analgesic and amnesic properties, along with dissociation. Thus, agents such as droperidol, fentanyl, nitrous oxide or ketamine were used. Although cardiovascular stability was achieved with the technique, airway management was still necessary, and perhaps because of the high incidence of recall, and problems with hallucination and emergence associated with some of the drugs, and the specific side effects (e.g. malignant neuroleptic syndrome) the method is rarely used.

Target-controlled infusions

Propofol is especially amenable to a total intravenous anaesthesia, a technique conventionally achieved by simply infusing the drug via a syringe pump at a predetermined rate (mg/hour or ml/hour) based on body weight. One problem with this method was that, if the pump infusion rate was increased from, for example, 10 ml/hour to 20 ml/hour, the change would not be instantaneously reflected in the blood or brain concentration. Improvements in pump technology, along with better estimations of effect site concentrations (i.e. concentration of agent in the brain for any given blood concentration) facilitated the development of target-controlled infusions. With this technique, the anaesthetist simply sets the initial target blood (or effect site) concentration required: the target concentration is achieved and maintained with no further intervention required by the user. Nomograms from clinical studies (and the operators’ own clinical experience) are used to correlate blood (or effect site) concentrations with clinical effect. The blood (or effect site) concentrations displayed by the pump are estimates from large trials relating infusion dosages with blood concentrations.

Summary of properties of intravenous anaesthetic agents

Agent	Type of drug	pKa	pH	Protein binding (%)	Clearance (ml/kg/min)	Volume of distribution (litre/kg)	Induction dose (mg/kg)	CVS effect	RS effects	Particular use	Side effects
Propofol	Propylphenol	n/a	7.0	90	25	1.5	2.0	CO ↓ Vasodilates BP ↓	↓	Facilitates LMA TIVA/TCI Day case/ICU	Acidosis in ICU children
Thiopental	Thiobarbiturate	7.6	10.6	80	4	2.5	4.0	CO → Venodilates BP ↓	↓	Anti-convulsant ICP ↓	Histamine release Accumulation Porphyria
Methohexital	Oxybarbiturate	7.9	10.5	75	11	2.2	2.0	CO → Vasodilates BP ↓	Apnoea	Day case ECT	Convulsions
Ketamine	Phencyclidine	7.5	~4.0	50	20	3.0	2.0	CO ↑ BP ↑	→	Hypovolaemia	Sympathomimetic Convulsions Hallucinations
Etomidate	Imidazole	4.2	8.0	75	20	4.0	0.3	CO → BP →	→/↓	Hypovolaemia Cardiac disease	PNV Steroid ↓
Diazepam	Benzodiazepine	3.3	3.5	–	0.5	1.0	n/a	CO → BP →	→/↓	Sedation Amnesia Anti-convulsant	Accumulation 'Hangover effect'
Midazolam	Benzodiazepine	6.2	7.0	–	10	1.5	0.01–0.40	CO → BP →	→/↓	Sedation Amnesia Co-induction Children premed	

BP, blood pressure; CO, cardiac output; CVS, cardiovascular system; ECT, electroconvulsive therapy; ICP, intracranial pressure; LMA, laryngeal mask airway; PNV, postoperative nausea and vomiting; n/a, data not relevant; RS, respiratory system; TIVA, total intravenous anaesthesia; TCI, target-controlled infusions; →, no change; ↓, decreased; ↑, increased

Table 2

The particular advantage of this method is that when the target concentration is increased, the pump delivers a very high (e.g. 1200 ml/hour) dose for a brief, calculated time to achieve a step-increase in blood concentration. This more accurate dosing potentially minimizes the total dose of anaesthetic used during surgery (thus also saving costs and adding to safety). One problem with the technique is that the concentration of anaesthetic in the blood is not directly measured, but only estimated from average population data.

Summary

Table 2 summarizes the salient features of the intravenous anaesthetic agents. Each agent has particular properties and for effective use in clinical practice, these are best tailored to each patient's condition and the requirements of the surgery. Whichever agent is used to induce anaesthesia, it is important to carefully titrate its action, especially with respect to cardiorespiratory and airway effects. ◆