General anaesthesia may be produced by many drugs which depress the CNS, including sedatives, tranquilizers and hypnotic agents. However, for some drugs the doses required to produce surgical anaesthesia are so large that cardiovascular and respiratory depression commonly occur, and recovery is delayed for hours or even days. Only a few drugs are suitable for use routinely to produce anaesthesia after intravenous (i.v.) injection.

Intravenous anaesthetic agents are used commonly to induce anaesthesia, as induction is usually smoother and more rapid than that associated with most of the inhalational agents. Intravenous anaesthetics may also be used for maintenance, either alone or in combination with nitrous oxide; they may be administered as repeated bolus doses or by continuous i.v. infusion. Other uses include sedation during regional anaesthesia, sedation in the intensive therapy unit (ITU) and treatment of status epilepticus.

**PROPERTIES OF THE IDEAL INTRAVENOUS ANAESTHETIC AGENT**

- Rapid onset – this is achieved by an agent which is mainly unionized at blood pH and which is highly soluble in lipid; these properties permit penetration of the blood–brain barrier
- Rapid recovery – early recovery of consciousness is usually produced by rapid redistribution of the drug from the brain into other well-perfused tissues, particularly muscle. The plasma concentration of the drug decreases, and the drug diffuses out of the brain along a concentration gradient. The quality of the later recovery period is related more to the rate of metabolism of the drug; drugs with slow metabolism are associated with a more prolonged ‘hangover’ effect and accumulate if used in repeated doses or by infusion for maintenance of anaesthesia
- Analgesia at subanaesthetic concentrations
- Minimal cardiovascular and respiratory depression
- No emetic effects
- No excitatory phenomena (e.g. coughing, hiccup, involuntary movement) on induction
- No emergence phenomena (e.g. nightmares)
- No interaction with neuromuscular blocking drugs
- No pain on injection
- No venous sequelae
- Safe if injected inadvertently into an artery
- No toxic effects on other organs
- No release of histamine
- No hypersensitivity reactions
- Water-soluble formulation
- Long shelf-life
- No stimulation of porphyria.

None of the agents available at present meets all these requirements. Features of the commonly used i.v. anaesthetic agents are compared in Table 3.1, and a classification of i.v. anaesthetic drugs is shown in Table 3.2.

**PHARMACOKINETICS OF INTRAVENOUS ANAESTHETIC DRUGS**

After i.v. administration of a drug, there is an immediate rapid increase in plasma concentration followed by a slower decline. Anaesthesia is produced by diffusion of drug from arterial blood across the blood–brain barrier into the brain. The rate of transfer into the brain, and therefore the anaesthetic effect, is regulated by the following factors:

**Protein binding.** Only unbound drug is free to cross the blood–brain barrier. Protein binding may be reduced by low plasma protein concentrations or displacement by other drugs, resulting in higher concentrations of free drug and an exaggerated anaesthetic effect. Protein binding is also affected by changes in blood pH. Hyperventilation decreases protein binding and increases the anaesthetic effect.

**Blood flow to the brain.** Reduced cerebral blood flow (CBF), e.g. carotid artery stenosis, results in reduced delivery of drug to the brain. However, if CBF is reduced
because of low cardiac output, initial blood concentrations are higher than normal after i.v. administration, and the anaesthetic effect may be delayed but enhanced.

*Extracellular pH and pKₐ of the drug.* Only the non-ionized fraction of the drug penetrates the lipid blood-brain barrier; thus, the potency of the drug depends on the degree of ionization at the pH of extracellular fluid and the pKₐ of the drug.

*The relative solubilities of the drug in lipid and water.* High lipid solubility enhances transfer into the brain.

*Speed of injection.* Rapid i.v. administration results in high initial concentrations of drug. This increases

<table>
<thead>
<tr>
<th>Table 3.1 Main properties of intravenous anaesthetics</th>
</tr>
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<tbody>
<tr>
<td>Physical properties</td>
</tr>
<tr>
<td>Water-soluble</td>
</tr>
<tr>
<td>Stable in solution</td>
</tr>
<tr>
<td>Long shelf-life</td>
</tr>
<tr>
<td>Pain on i.v. injection</td>
</tr>
<tr>
<td>Non-irritant on s.c. injection</td>
</tr>
<tr>
<td>Painful on arterial injection</td>
</tr>
<tr>
<td>No sequelae from intra-arterial injection</td>
</tr>
<tr>
<td>Low incidence of venous thrombosis</td>
</tr>
<tr>
<td>Effects on body</td>
</tr>
<tr>
<td>Recovery due to:</td>
</tr>
<tr>
<td>Redistribution</td>
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<tr>
<td>Detoxification</td>
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<tr>
<td>Cumulation</td>
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<tr>
<td>Induction</td>
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<tr>
<td>Excitatory effects</td>
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<tr>
<td>Respiratory complications</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Analgesic</td>
</tr>
<tr>
<td>Antanalgesic</td>
</tr>
<tr>
<td>Interaction with relaxants</td>
</tr>
<tr>
<td>Postoperative vomiting</td>
</tr>
<tr>
<td>Emergence delirium</td>
</tr>
<tr>
<td>Safe in porphyria</td>
</tr>
</tbody>
</table>

^aAqueous solution not commercially available.

^bPain may be reduced when emulsion with medium-chain triglycerides is used.
the speed of induction, but also the extent of cardiovascular and respiratory side-effects.

In general, any factor which increases the blood concentration of free drug, e.g. reduced protein binding or low cardiac output, also increases the intensity of side-effects.

Distribution to other tissues

The anaesthetic effect of all i.v. anaesthetic drugs in current use is terminated predominantly by distribution to other tissues. Figure 3.1 shows this distribution for thiopental. The percentage of the injected dose in each of four body compartments as time elapses is shown after i.v. injection. A large proportion of the drug is distributed initially into well-perfused organs (termed the vessel-rich group, or viscera – predominantly brain, liver and kidneys). Distribution into muscle (lean) is slower because of its low lipid content, but it is quantitatively important because of its relatively good blood supply and large mass. Despite their high lipid solubility, i.v. anaesthetic drugs distribute slowly to adipose tissue (fat) because of its poor blood supply. Fat contributes little to the initial redistribution or termination of action of i.v. anaesthetic agents, but fat depots contain a large proportion of the injected dose of thiopental at 90 min, and 65–75% of the total remaining in the body at 24 h. There is also a small amount of redistribution to areas with a very poor blood supply, e.g. bone. Table 3.3 indicates some of the properties of the body compartments in respect of the distribution of i.v. anaesthetic agents.

After a single i.v. dose, the concentration of drug in blood decreases as distribution occurs into viscera, and particularly muscle. Drug diffuses from the brain into blood along the changing concentration gradient, and recovery of consciousness occurs. Metabolism of most i.v. anaesthetic drugs occurs predominantly in the liver. If metabolism is rapid (indicated by a short

| Table 3.3 Factors influencing the distribution of thiopental in the body |
|-----------------|----------------|-------------|-------------|-------------|
|                | Viscera | Muscle | Fat | Others |
| Relative blood flow | Rich   | Good   | Poor | Very poor |
| Blood flow (L min⁻¹) | 4.5    | 1.1    | 0.32 | 0.08        |
| Tissue volume (L; A) | 6      | 33     | 15  | 13          |
| Tissue/blood partition coefficient (B) | 1.5 | 1.5 | 11.0 | 1.5 |
| Potential capacity (L; A × B) | 9     | 50     | 160 | 20          |
| Time constant (capacity/flow; min) | 2     | 45     | 500 | 250        |
elimination half-life), it may contribute to some extent to the recovery of consciousness. However, because of the large distribution volume of i.v. anaesthetic drugs, total elimination takes many hours, or, in some instances, days. A small proportion of drug may be excreted unchanged in the urine; the amount depends on the degree of ionization and the pH of urine.

**BARBITURATES**

Amobarbital and pentobarbital were used i.v. to induce anaesthesia in the late 1920s, but their actions were unpredictable and recovery was prolonged. Manipulation of the barbituric acid ring (Fig. 3.2) enabled a short duration of action to be achieved by:

- substitution of a sulphur atom for oxygen at position 2
- substitution of a methyl group at position 1; this also confers potential convulsive activity and increases the incidence of excitatory phenomena.

An increased number of carbon atoms in the side chains at position 5 increases the potency of the agent. The presence of an aromatic nucleus in an alkyl group at position 5 produces compounds with convulsant properties; direct substitution with a phenyl group confers anticonvulsant activity.

The anaesthetically active barbiturates are classified chemically into four groups (Table 3.4). The methylated oxybarbiturate hexobarbital was moderately successful as an i.v. anaesthetic agent, but was superseded by the development in 1932 of thiopental. Although propofol has become very popular in a number of countries, thiopental remains one of the most commonly used i.v. anaesthetic agents throughout the world. Its pharmacology is therefore described fully in this chapter. Many of its effects are shared by other i.v. anaesthetic agents and consequently the pharmacology of these drugs is described more briefly.

**THIOPENTAL SODIUM**

**Chemical structure**

Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.

**Physical properties and presentation**

Thiopental sodium, the sulphur analogue of pentobarbital, is a yellowish powder with a bitter taste and a faint smell of garlic. It is stored in nitrogen to prevent chemical reaction with atmospheric carbon dioxide, and mixed with 6% anhydrous sodium carbonate to

<table>
<thead>
<tr>
<th>Table 3.4 Relation of chemical grouping to clinical action of barbiturates</th>
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</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Oxybarbiturates</td>
</tr>
<tr>
<td>Methyl barbiturates</td>
</tr>
<tr>
<td>Thiobarbiturates</td>
</tr>
<tr>
<td>Methyl thiobarbiturates</td>
</tr>
</tbody>
</table>
INTRAVENOUS ANAESTHETIC AGENTS

increase its solubility in water. It is available in single-dose ampoules of 500 mg and is dissolved in distilled water to produce 2.5% (25 mg ml\(^{-1}\)) solution with a pH of 10.8; this solution is slightly hypotonic. Freshly prepared solution may be kept for 24 h. The oil/water partition coefficient of thiopental is 4.7, and the \( pK_a \) 7.6.

**Central nervous system**

Thiopental produces anaesthesia usually less than 30 s after i.v. injection, although there may be some delay in patients with a low cardiac output. There is progressive depression of the CNS, including spinal cord reflexes. The hypnotic action of thiopental is potent, but its analgesic effect is poor, and surgical anaesthesia is difficult to achieve unless large doses are used; these are associated with cardiorespiratory depression. The cerebral metabolic rate is reduced and there are secondary decreases in CBF, cerebral blood volume and intracranial pressure. Recovery of consciousness occurs at a higher blood concentration if a large dose is given, or if the drug is injected rapidly; this has been attributed to acute tolerance, but may represent only altered redistribution. Consciousness is usually regained in 5-10 min. At subanaesthetic blood concentrations (i.e. at low doses or during recovery), thiopental has an analgesic effect and reduces the pain threshold; this may result in restlessness in the postoperative period. Thiopental is a very potent anticonvulsant.

Sympathetic nervous system activity is depressed to a greater extent than parasympathetic; this may occasionally result in bradycardia. However, it is more usual for tachycardia to develop after induction of anaesthesia, partly because of baroreceptor inhibition caused by modest hypotension and partly because of loss of vagal tone which may predominate normally in young healthy adults.

**Cardiovascular system**

Myocardial contractility is depressed and peripheral vasodilatation occurs, particularly when large doses are administered or if injection is rapid. Arterial pressure decreases, and profound hypotension may occur in the patient with hypovolaemia or cardiac disease. Heart rate may decrease, but there is often a reflex tachycardia (see above).

**Respiratory system**

Ventilatory drive is decreased by thiopental as a result of reduced sensitivity of the respiratory centre to carbon dioxide. A short period of apnoea is common, frequently preceded by a few deep breaths. Respiratory depression is influenced by premedication and is more pronounced if opioids have been administered; assisted or controlled ventilation may be required. When spontaneous ventilation is resumed, ventilatory rate and tidal volume are usually lower than normal, but they increase in response to surgical stimulation. There is an increase in bronchial muscle tone, although frank bronchospasm is uncommon.

Laryngeal spasm may be precipitated by surgical stimulation or the presence of secretions, blood or foreign bodies (e.g. an oropharyngeal or laryngeal mask airway) in the region of the pharynx or larynx. Thiopental is less satisfactory in this respect than propofol, and appears to depress the parasympathetic laryngeal reflex arc to a lesser extent than other areas of the CNS.

**Skeletal muscle**

Skeletal muscle tone is reduced at high blood concentrations, partly as a result of suppression of spinal cord reflexes. There is no significant direct effect on the neuromuscular junction. When thiopental is used as the sole anaesthetic agent, there is poor muscle relaxation, and movement in response to surgical stimulation is common.

**Uterus and placenta**

There is little effect on resting uterine tone, but uterine contractions are suppressed at high doses. Thiopental crosses the placenta readily, although fetal blood concentrations do not reach the same levels as those observed in the mother.

**Eye**

Intraocular pressure is reduced by approximately 40%. The pupil dilates first, and then constricts; the light reflex remains present until surgical anaesthesia has been attained. The corneal, conjunctival, eyelash and eyelid reflexes are abolished.

**Hepatorenal function**

The functions of the liver and kidneys are impaired transiently after administration of thiopental. Hepatic microsomal enzymes are induced and this may increase the metabolism and elimination of other drugs.

**Pharmacokinetics**

Blood concentrations of thiopental increase rapidly after i.v. administration. Between 75 and 85% of the
drug is bound to protein, mostly albumin; thus, more free drug is available if plasma protein concentrations are reduced by malnutrition or disease. Protein binding is affected by pH and is decreased by alkalaeemia; thus, the concentration of free drug is increased during hyperventilation. Some drugs, e.g. phenylbutazone, occupy the same binding sites, and protein binding of thiopental may be reduced in their presence.

Thiopental diffuses readily into the CNS because of its lipid solubility and predominantly unionized state (61%) at body pH. Consciousness returns when the brain concentration decreases to a threshold value, dependent on the individual patient, the dose of drug and its rate of administration, but at this time nearly all of the injected dose is still present in the body.

Metabolism of thiopental occurs predominantly in the liver, and the metabolites are excreted by the kidneys; a small proportion is excreted unchanged in the urine. The terminal elimination half-life is approximately 11.5 h. Metabolism is a zero-order process; 10–15% of the remaining drug is metabolized each hour. Thus, up to 30% of the original dose may remain in the body at 24 h. Consequently, a ‘hangover’ effect is common; in addition, further doses of thiopental administered within 1–2 days may result in cumulation. Elimination is impaired in the elderly. In obese patients, dosage should be based on an estimate of lean body mass, as distribution to fat is slow. However, elimination may be delayed in obese patients because of increased retention of the drug by adipose tissue.

**Dosage and administration**

Thiopental is administered i.v. as a 2.5% solution; the use of a 5% solution increases the likelihood of serious complications and is not recommended. A small volume, e.g. 1–2 mL in adults, should be administered initially; the patient should be asked if any pain is experienced in case of inadvertent intra-arterial injection (see below) before the remainder of the induction dose is given.

The dose required to produce anaesthesia varies, and the response of each patient must be assessed carefully; cardiovascular depression is exaggerated if excessive doses are given. In healthy adults, an initial dose of 4 mg Kg$^{-1}$ should be administered over 15–20 s; if loss of the eyelash reflex does not occur within 30 s, supplementary doses of 50–100 mg should be given slowly until consciousness is lost. In young children, a dose of 6 mg kg$^{-1}$ is usually necessary. Elderly patients often require smaller doses (e.g. 2.5–3 mg kg$^{-1}$) than young adults.

Induction is usually smooth and may be preceded by a taste of garlic. Side-effects are related to peak blood concentrations, and in patients in whom cardiovascular depression may occur the drug should be administered more slowly; in very frail patients, as little as 50 mg may be sufficient to induce sleep.

No other drug should be mixed with thiopental. Muscle relaxants should not be given until it is certain that anaesthesia has been induced. The i.v. cannula should be flushed with saline before vecuronium or atracurium is administered, to obviate precipitation.

Supplementary doses of 25–100 mg may be given to augment nitrous oxide/oxygen anaesthesia during short surgical procedures. However, recovery may be prolonged considerably if large total doses are used (>10 mg kg$^{-1}$).

**Adverse effects**

**Hypotension.** The risk is increased if excessive doses are used, or if thiopental is administered to hypovolaemic, shocked or previously hypertensive patients. Hypotension is minimized by administering the drug slowly. Thiopental should not be administered to patients in the sitting position.

**Respiratory depression.** The risk is increased if excessive doses are used, or if opioid drugs have been administered. Facilities must be available to provide artificial ventilation.

**Tissue necrosis.** Local necrosis may follow perivene nous injection. Median nerve damage may occur after extravasation in the antecubital fossa, and this site is not recommended. If periveneous injection occurs, the needle should be left in place and hyaluronidase injected.

**Intra-arterial injection.** This is usually the result of inadvertent injection into the brachial artery or an aberrant ulnar artery in the antecubital fossa but has occurred occasionally into aberrant arteries at the wrist. The patient usually complains of intense, burning pain, and this is an indication to stop injecting the drug immediately. The forearm and hand may become blanched and blisters may appear distally. Intra-arterial thiopental causes profound constriction of the artery accompanied by local release of norepinephrine. In addition, crystals of thiopental form in arteries. In combination with thrombosis caused by endarteritis, adenosine triphosphate release from damaged red cells and aggregation of platelets, these result in emboli and may cause ischaemia or gangrene in parts of the forearm, hand or fingers.

The needle should be left in the artery and a vasodilator (e.g. papaverine 20 mg) administered. Stellate ganglion or brachial plexus block may reduce arterial spasm. Heparin should be given i.v. and oral anticoagulants should be prescribed after operation.
The risk of ischaemic damage after intra-arterial injection is much greater if a 5% solution of thiopental is used.

**Laryngeal spasm.** The causes have been discussed above.

**Bronchospasm.** This is unusual, but may be precipitated in asthmatic patients.

**Allergic reactions.** These range from cutaneous rashes to severe or fatal anaphylactic or anaphylactoid reactions with cardiovascular collapse. Severe reactions are rare (approximately 1 in 14 000–20 000). Hypersensitivity reactions to drugs administered during anaesthesia are discussed on page 50.

**Thrombophlebitis.** This is uncommon (Table 3.5) when the 2.5% solution is used.

**Indications**
- induction of anaesthesia
- maintenance of anaesthesia – thiopental is suitable only for short procedures because cumulation occurs with repeated doses
- treatment of status epilepticus
- reduction of intracranial pressure (see Ch. 38).

**Absolute contraindications**
- Airway obstruction – intravenous anaesthesia should not be used if there is anticipated difficulty in maintaining an adequate airway, e.g. epiglottitis, oral or pharyngeal tumours.
- Porphyria – barbiturates may precipitate lower motor neurone paralysis or severe cardiovascular collapse in patients with porphyria.
- Previous hypersensitivity reaction to a barbiturate.

**Precautions**
Special care is needed when thiopental is administered in the following circumstances:

**Cardiovascular disease.** Patients with hypovolaemia, myocardial disease, cardiac valvular stenosis or constrictive pericarditis are particularly sensitive to the hypotensive effects of thiopental. However, if the drug is administered with extreme caution, it is probably no more hazardous than other i.v. anaesthetic agents. Myocardial depression may be severe in patients with right-to-left intracardiac shunt because of high coronary artery concentrations of thiopental.

**Severe hepatic disease.** Reduced protein binding results in higher concentrations of free drug. Metabolism may be impaired, but this has little effect on early recovery. A normal dose may be administered, but very slowly.

**Renal disease.** In chronic renal failure, protein binding is reduced, but elimination is unaltered. A normal dose may be administered, but very slowly.

**Muscle disease.** Respiratory depression is exaggerated in patients with myasthenia gravis or dystrophia myotonica.

**Reduced metabolic rate.** Patients with myxoedema are exquisitely sensitive to the effects of thiopental.

**Obstetrics.** An adequate dose must be given to ensure that the mother is anaesthetized. However, excessive doses may result in respiratory or cardiovascular depression in the fetus, particularly if the interval between induction and delivery is short.

**Outpatient anaesthesia.** Early recovery is slow in comparison with other agents. This is seldom important unless rapid return of airway reflexes is essential, e.g. after oral or dental surgery. However, slow elimination of thiopental may result in persistent drowsiness for 24–36 h, and this impairs the ability to drive or use machinery. There is also potentiation of the effect of alcohol or sedative drugs ingested during that period. It is preferable to use a drug with more rapid elimination for patients who are ambulant within a few hours.

**Adrenocortical insufficiency.**

**Extremes of age.**

**Asthma.**

**METHOHEXITAL SODIUM**

**Chemical structure**
Sodium α-dl-5-allyl-1-methyl-5-(1-methyl-2-pentynyl) barbiturate.

**Physical properties and presentation**
Although no longer available in the United Kingdom, methohexital is still used in a number of other countries. The drug has two asymmetrical carbon atoms, and therefore four isomers. The α-dl isomers are clinically useful. The drug is presented as a white powder mixed with 6% anhydrous sodium carbonate and is readily soluble in distilled water. The resulting 1% (10 mg mL⁻¹) solution has a pH of 11.1 and pKₐ of 7.9. Single-dose vials of 100 mg and multidose bottles containing 500 mg or 2.5 g are available in some countries. Although the solution is chemically stable for up to 6 weeks, the manufacturers recommend that it should not be stored for longer than 24 h because it does not contain antibacterial preservative.
Pharmacology

Central nervous system

Unconsciousness is usually induced in 15–30 s. Recovery is more rapid with methohexital than with thiopental, and occurs after 2–3 min; it is caused predominantly by redistribution. Drowsiness may persist for several hours until blood concentrations are decreased further by metabolism. Epileptiform activity has been demonstrated by EEG in epileptic patients. However, in sufficient doses, methohexital acts as an anticonvulsant.

Cardiovascular system

In general, there is less hypotension in otherwise healthy patients than occurs after thiopental; the decrease in arterial pressure is mediated predominantly by vasodilatation. Heart rate may increase slightly because of a decrease in baroreceptor activity. The cardiovascular effects are more pronounced in patients with cardiac disease or hypovolaemia.

Respiratory system

Moderate hypoventilation occurs. There may be a short period of apnoea after i.v. injection.

Pharmacokinetics

A greater proportion of methohexital than thiopental is in the unionized state at body pH (approximately 75%), although the drug is less lipid-soluble than the thiobarbiturate. Binding to plasma protein occurs to a similar degree. Clearance from plasma is higher than that of thiopental, and the elimination half-life is considerably shorter (approximately 4 h). Thus, accumulation is less likely to occur after repeated doses.

Dosage and administration

Methohexital is administered i.v. in a dose of 1–1.5 mg kg$^{-1}$ to induce anaesthesia in healthy young adult patients; smaller doses are required in the elderly and infirm.

Adverse effects

Cardiovascular and respiratory depression. This is probably less than that associated with thiopental.

Excitatory phenomena during induction, including dyskinetic muscle movements, coughing and hiccups. Muscle movements are reduced by administration of an opioid; the incidence of cough and hiccups is reduced by premedication with an anticholinergic agent. The incidence of excitatory effects is dose-related.

Epileptiform activity on EEG in epileptic subjects.

Pain on injection (Table 3.5).

Tissue damage after perivenuous injection is rare with 1% solution.

Intra-arterial injection may cause gangrene, but the risk with 1% solution is considerably less than with 2.5% thiopental.

Allergic reactions occur, but are uncommon.

Thrombophlebitis is a rare complication.

Indications

Induction of anaesthesia, particularly when a rapid recovery is desirable. Methohexital has been used commonly as the anaesthetic agent for electroconvulsive therapy (ECT) and for induction of anaesthesia for outpatient dental and other minor procedures.

Absolute contraindications

These are the same as for thiopental.

Precautions

These are similar to the precautions listed for thiopental. However, methohexital is a suitable agent for outpatients. It should not be used to induce anaesthesia in patients who are known to be epileptic.

THIAMYLAL SODIUM

This is a sulphur analogue of quinalbarbital. It is slightly more potent than thiopental, but otherwise almost identical in its properties. It is not available in the UK, but is used in some other countries.

NON-BARBITURATE INTRAVENOUS ANAESTHETIC AGENTS

PROPOFOL

This phenol derivative was identified as a potentially useful intravenous anaesthetic agent in 1980, and became available commercially in 1986. It has achieved great popularity because of its favourable recovery characteristics and its antiemetic effect.

Chemical structure

2,6-Di-isopropylphenol (Fig. 3.3).
INTRAVENOUS ANAESTHETIC AGENTS

Physical properties and presentation

Propofol is extremely lipid-soluble, but almost insoluble in water. The drug was formulated initially in Cremophor EL. However, several other drugs formulated in this solubilizing agent were associated with release of histamine and an unacceptably high incidence of anaphylactoid reactions, and similar reactions occurred with this formulation of propofol. Consequently, the drug was reformulated in a white, aqueous emulsion containing soyabean oil and purified egg phosphatide. Ampoules of the drug contain 200 mg of propofol in 20 mL (10 mg mL$^{-1}$), and 50 mL bottles containing 1% (10 mg mL$^{-1}$) or 2% (20 mg mL$^{-1}$) solution, and 100 mL bottles containing 1% solution, are available for infusion. In addition, 50 mL prefilled syringes of 1 and 2% solution are available and are designed for use in target-controlled infusion techniques (see below).

Pharmacology

**Central nervous system**

Anaesthesia is induced within 20–40 s after i.v. administration in otherwise healthy young adults. Transfer from blood to the sites of action in the brain is slower than with thiopental, and there is a delay in disappearance of the eyelash reflex, normally used as a sign of unconsciousness after administration of barbiturate anaesthetic agents. Overdosage of propofol, with exaggerated side-effects, may result if this clinical sign is used; loss of verbal contact is a better end-point. EEG frequency decreases, and amplitude increases. Propofol reduces the duration of seizures induced by ECT in humans. However, there have been reports of convulsions following the use of propofol and it is recommended that caution be exercised in the administration of propofol to epileptic patients. Normally cerebral metabolic rate, CBF and intracranial pressure are reduced.

Recovery of consciousness is rapid and there is a minimal ‘hangover’ effect even in the immediate postanaesthetic period.

Table 3.5 Percentage incidences of pain on injection and thrombophlebitis after intravenous administration of anaesthetic drugs into a large vein in the antecubital fossa or a small vein in the dorsum of the hand or wrist

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pain</th>
<th>Thrombophlebitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Saline 0.9%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thiopental 2.5%</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Methohexital 1%</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Propofol – LCT emulsion</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Propofol – MCT emulsion</td>
<td>n/a</td>
<td>15</td>
</tr>
<tr>
<td>Etomidate – propylene glycol</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Etomidate – MCT emulsion</td>
<td>n/a</td>
<td>4</td>
</tr>
</tbody>
</table>

MCT = medium-chain triglyceride, LCT = long-chain triglyceride.

Fig. 3.3

Chemical structure of propofol (2,6-di-isopropylphenol).
**Cardiovascular system**

In healthy patients, arterial pressure decreases to a greater degree after induction of anaesthesia with propofol than with thiopental; the reduction results predominantly from vasodilatation although there is a slight negative inotropic effect. In some patients, large decreases (>40%) occur. The degree of hypotension is substantially reduced by decreasing the rate of administration of the drug and by appreciation of the kinetics of transfer from blood to brain (see above). The pressor response to tracheal intubation is attenuated to a greater degree by propofol than thiopental. Heart rate may increase slightly after induction of anaesthesia with propofol. However, there have been occasional reports of severe bradycardia and asystole during or shortly after administration of propofol, and it is recommended that a vagolytic agent (e.g. glycopyrronium or atropine) should be considered in patients with a pre-existing bradycardia or when propofol is used in conjunction with other drugs which are likely to cause bradycardia.

**Respiratory system**

After induction, apnoea occurs more commonly, and for a longer duration, than after thiopental. During infusion of propofol, tidal volume is lower and respiratory rate higher than in the conscious state. There is decreased ventilatory response to carbon dioxide. As with other agents, ventilatory depression is more marked if opioids are administered.

Propofol has no effect on bronchial muscle tone and laryngospasm is particularly uncommon. The suppression of laryngeal reflexes results in a low incidence of coughing or laryngospasm when a laryngeal mask airway (LMA) is introduced, and propofol is regarded by most anaesthetists as the drug of choice for induction of anaesthesia when the LMA is to be used.

**Skeletal muscle**

Tone is reduced, but movements may occur in response to surgical stimulation.

**Gastrointestinal system**

Propofol has no effect on gastrointestinal motility in animals. Its use is associated with a low incidence of postoperative nausea and vomiting.

**Uterus and placenta**

Propofol has been used extensively in patients undergoing gynaecological surgery, and it does not appear to have any clinically significant effect on uterine tone. Propofol crosses the placenta. Its safety to the neonate has not been established and its use in pregnancy (except for termination), in obstetric practice and in breast-feeding mothers is not recommended by the manufacturers.

**Hepatorenal**

There is a transient decrease in renal function, but the impairment is less than that associated with thiopental. Hepatic blood flow is decreased by the reductions in arterial pressure and cardiac output. Liver function tests are not deranged after infusion of propofol for 24 h.

**Endocrine**

Plasma concentrations of cortisol are decreased after administration of propofol, but a normal response occurs to the administration of Synacthen.

**Pharmacokinetics**

In common with other i.v. anaesthetic drugs, propofol is distributed rapidly, and blood concentrations decline exponentially. Clearance of the drug from plasma is greater than would be expected if the drug was metabolized only in the liver, and it is believed that extrahepatic sites of metabolism exist. The kidneys excrete the metabolites of propofol (mainly glucuronides); only 0.3% of the administered dose of propofol is excreted unchanged. The terminal elimination half-life of propofol is 3–4.8 h, although its effective half-life is much shorter (30–60 min). The distribution and clearance of propofol are altered by concomitant administration of fentanyl. Elimination of propofol remains relatively constant even after infusions lasting for several days.

**Dosage and administration**

In healthy, unpremedicated adults, a dose of 1.5–2.5 mg kg$^{-1}$ is required to induce anaesthesia. The dose should be reduced in the elderly; an initial dose of 1.25 mg kg$^{-1}$ is appropriate, with subsequent additional doses of 10 mg until consciousness is lost. In children, a dose of 3–3.5 mg kg$^{-1}$ is usually required; the drug is not recommended for use in children less than 1 month of age. Cardiovascular side-effects are reduced if the drug is injected slowly. Lower doses are required for induction in premedicated patients. Sedation during regional analgesia or endoscopy may be achieved with infusion rates of 1.5–4.5 mg kg$^{-1}$ h$^{-1}$. 
Infusion rates of up to $15 \text{ mg kg}^{-1} \text{ h}^{-1}$ are required to supplement nitrous oxide/oxygen for surgical anaesthesia, although these may be reduced substantially if an opioid drug is administered. The average infusion rate is approximately $2 \text{ mg kg}^{-1} \text{ h}^{-1}$ in conjunction with a slow infusion of morphine ($2 \text{ mg h}^{-1}$) for sedation of patients in ICU.

**Adverse effects**

*Cardiovascular depression.* Unless the drug is given very slowly, cardiovascular depression following a bolus dose of propofol is greater than that associated with a bolus dose of a barbiturate and is likely to cause profound hypotension in hypovolaemic or untreated hypertensive patients and in those with cardiac disease. Cardiovascular depression is modest if the drug is administered slowly or by infusion.

*Respiratory depression.* Apnoea is more common and of longer duration than after barbiturate administration.

*Excitatory phenomena.* These are more frequent on induction than with thiopental, but less than with methohexital. There have been occasional reports of convulsions and myoclonus during recovery from anaesthesia in which propofol has been used. Some of these reactions are delayed.

*Pain on injection.* This occurs in up to 40% of patients (Table 3.5). The incidence is greatly reduced if a large vein is used, if a small dose (10 mg) of lidocaine is injected shortly before propofol, or if lidocaine is mixed with propofol in the syringe (up to 1 mL of 0.5 or 1% lidocaine per 20 mL of propofol). A preparation of propofol in an emulsion of medium-chain triglycerides and soya (Propofol-Lipuro®) causes a lower incidence of pain, and less severe pain in those who still experience it, than other formulations (which use long-chain triglycerides) and may obviate the need for lidocaine. Accidental extravasation or intra-arterial injection of propofol does not appear to result in adverse effects.

*Allergic reactions.* Skin rashes occur occasionally. Anaphylactic reactions have also been reported, but appear to be less common than with thiopental.

**Indications**

*Induction of anaesthesia.* Propofol is indicated particularly when rapid early recovery of consciousness is required. Two hours after anaesthesia, there is no difference in psychomotor function between patients who have received propofol and those given thiopental or methohexital, but the former enjoy less drowsiness in the ensuing 12 h. The rapid recovery characteristics are lost if induction is followed by maintenance with inhalational agents for longer than 10–15 min. The rapid redistribution and metabolism of propofol may increase the risks of awareness during tracheal intubation after the administration of non-depolarizing muscle relaxants, or at the start of surgery, unless the lungs are ventilated with an appropriate mixture of inhaled anaesthetics, or additional doses or an infusion of propofol administered.

*Sedation during surgery.* Propofol has been used successfully for sedation during regional analgesic techniques and during endoscopy. Control of the airway may be lost at any time, and patients must be supervised continuously by an anaesthetist.

*Total i.v. anaesthesia (see below).* Propofol is the most suitable of the agents currently available. Recovery time is increased after infusion of propofol compared with that after a single bolus dose, but cumulation is significantly less than with the barbiturates.

*Sedation in ICU.* Propofol has been used successfully by infusion to sedate adult patients for several days in ICU. The level of sedation is controlled easily, and recovery is rapid (usually < 30 min).

**Absolute contraindications**

Airway obstruction and known hypersensitivity to the drug are probably the only absolute contraindications. Propofol appears to be safe in porphyric patients. Propofol should not be used for long-term sedation of children (under 17 years of age) in the ICU because of a number of reports of adverse outcome.

**Precautions**

These are similar to those listed for thiopental. The side-effects of propofol make it less suitable than thiopental or methohexital for patients with existing cardiovascular compromise unless it is administered with great care. Propofol is more suitable than thiopental for outpatient anaesthesia, but its use does not obviate the need for an adequate period of recovery before discharge.

Solutions of propofol do not possess any antibacterial properties, and they support the growth of microorganisms. The drug must be drawn aseptically into a syringe and any unused solution should be discarded if not administered promptly. Propofol must not be administered via a microbiological filter.

**ETOMIDATE**

This carboxylated imidazole compound was introduced in 1972.
Chemical structure
D-Ethyl-1-(α-methylbenzyl)-imidazole-5-carboxylate.

Physical characteristics and presentation
Etomidate is soluble but unstable in water. It is presented as a clear aqueous solution containing 35% propylene glycol, or in an emulsion preparation with medium-chain triglycerides and soya-bean oil. Ampoules contain 20 mg of etomidate in 10 mL (2 mg mL⁻¹). The pH of the propylene glycol solution is 8.1.

Pharmacology
Etomidate is a rapidly acting general anaesthetic agent with a short duration of action (2–3 min) resulting predominantly from redistribution, although it is also eliminated rapidly from the body. In healthy patients, it produces less cardiovascular depression than does thiopental; however, there is little evidence that this benefit is retained if the cardiovascular system is compromised. Large doses may produce tachycardia. Respiratory depression is less than with other agents.

Etomidate depresses the synthesis of cortisol by the adrenal gland and impairs the response to adrenocorticotropic hormone. Long-term infusions of the drug in the ICU have been associated with increased infection and mortality, probably related to reduced immunological competence. Its effects on the adrenal gland occur also after a single bolus, and last for several hours.

Pharmacokinetics
Etomidate redistributes rapidly in the body. Approximately 76% is bound to protein. It is metabolized in the plasma and liver, mainly by esterase hydrolysis, and the metabolites are excreted in the urine; 2% is excreted unchanged. The terminal elimination half-life is 2.4–5 h. There is little cumulation when repeated doses are given. The distribution and clearance of etomidate may be altered by concomitant administration of fentanyl.

Dosage and administration
An average dose of 0.3 mg kg⁻¹ i.v. induces anaesthesia. The propylene glycol preparation of the drug should be administered into a large vein to reduce the incidence of pain on injection.

Adverse effects
Suppression of synthesis of cortisol. See above.

Excitatory phenomena. Moderate or severe involuntary movements occur in up to 40% of patients during induction of anaesthesia. This incidence is reduced in patients premedicated with an opioid. Cough and hiccup occur in up to 10% of patients.

Pain on injection. This occurs in up to 80% of patients if the propylene glycol preparation is injected into a small vein, but in less than 10% when the drug is injected into a large vein in the antecubital fossa (Table 3.5). The incidence is reduced by prior injection of lidocaine 10 mg. The incidence of pain on injection has been reported to be as low as 4% when the emulsion formulation is injected.

Nausea and vomiting. The incidence of nausea and vomiting is approximately 30%. This is very much higher than after propofol.

Emergence phenomena. The incidence of severe restlessness and delirium during recovery is greater with etomidate than barbiturates or propofol.

Venous thrombosis is more common than with other agents.

Indications
Etomidate is used by many anaesthetists in patients with a compromised cardiovascular system. It is suitable for outpatient anaesthesia. The high incidence of pain on injection of the propylene glycol preparation of etomidate limited its use to patients in whom depression of the cardiovascular system was undesirable, but the preparation as an emulsion with medium-chain triglycerides has greatly reduced the incidence of pain on injection and is likely to result in increased use of the drug in all patient groups.

Absolute contraindications
- airway obstruction
- porphyria
- adrenal insufficiency
- long-term infusion in ITU.

Precautions
These are similar to the precautions listed for thiopental. Etomidate is suitable for outpatient anaesthesia. However, the incidence of excitatory phenomena is unacceptable high unless an opioid is administered; this delays recovery and is unsuitable for most outpatients.

KETAMINE HYDROCHLORIDE
This is a phencyclidine derivative and was introduced in 1965. It differs from other i.v. anaesthetic agents in
many respects, and produces dissociative anaesthesia rather than generalized depression of the CNS.

**Chemical structure**

2-(o-Chlorophenyl)-2-(methylamino)-cyclohexanone hydrochloride.

**Physical characteristics and presentation**

Ketamine is soluble in water and is presented as solutions of 10 mg mL\(^{-1}\) containing sodium chloride to produce isotonicity, and 50 or 100 mg mL\(^{-1}\) in multidose vials which contain benzethonium chloride 0.1 mg mL\(^{-1}\) as preservative. The pH of the solutions is 3.5–5.5. The \(pK_a\) of ketamine is 7.5.

**Pharmacology**

**Central nervous system**

Ketamine is extremely lipid-soluble. After i.v. injection, it induces anaesthesia in 30–60 s. A single i.v. dose produces unconsciousness for 10–15 min. Ketamine is also effective within 3–4 min after i.m. injection and has a duration of action of 15–25 min. It is a potent somatic analgesic at subanaesthetic blood concentrations. Amnesia often persists for up to 1 h after recovery of consciousness. Induction of anaesthesia is smooth, but emergence delirium may occur, with restlessness, disorientation and agitation. Vivid and often unpleasant nightmares or hallucinations may occur during recovery and for up to 24 h. The incidences of emergence delirium and hallucinations are reduced by avoidance of verbal and tactile stimulation during the recovery period, or by concomitant administration of opioids, butyrophenones, benzodiazepines or physostigmine; however, unpleasant dreams may persist. Nightmares are reported less commonly by children and elderly patients.

The EEG changes associated with ketamine are unlike those seen with other i.v. anaesthetics, and consist of loss of alpha rhythm and predominant theta activity. Cerebral metabolic rate is increased in several regions of the brain, and CBF, cerebral blood volume and intracranial pressure increase.

**Cardiovascular system**

Arterial pressure increases by up to 25% and heart rate by approximately 20%. Cardiac output may increase, and myocardial oxygen consumption increases; the positive inotropic effect may be related to increased calcium influx mediated by cyclic adenosine monophosphate. There is increased myocardial sensitivity to epinephrine. Sympathetic stimulation of the peripheral circulation is decreased, resulting in vasodilatation in tissues innervated predominantly by \(\alpha\)-adrenergic receptors, and vasoconstriction in those with \(\beta\)-receptors.

**Respiratory system**

Transient apnoea may occur after i.v. injection, but ventilation is well maintained thereafter and may increase slightly unless high doses are given. Pharyngeal and laryngeal reflexes and a patent airway are maintained well in comparison with other i.v. agents; however, their presence cannot be guaranteed, and normal precautions must be taken to protect the airway and prevent aspiration. Bronchial muscle is dilated.

**Skeletal muscle**

Muscle tone is usually increased. Spontaneous movements may occur, but reflex movement in response to surgery is uncommon.

**Gastrointestinal system**

Salivation is increased.

**Uterus and placenta**

Ketamine crosses the placenta readily. Fetal concentrations are approximately equal to those in the mother.

**The eye**

Intraocular pressure increases, although this effect is often transient. Eye movements often persist during surgical anaesthesia.

**Pharmacokinetics**

Only approximately 12% of ketamine is bound to protein. The initial peak concentration after i.v. injection decreases as the drug is distributed, but this occurs more slowly than with other i.v. anaesthetic agents. Metabolism occurs predominantly in the liver by demethylation and hydroxylation of the cyclohexanone ring; among the metabolites is norketamine, which is pharmacologically active. Approximately 80% of the injected dose is excreted renally as glucuronides; only 2.5% is excreted unchanged. The elimination half-life is approximately 2.5 h. Distribution and elimination are slower if halothane, benzodiazepines or barbiturates are administered concurrently.

After i.m. injection, peak concentrations are achieved after approximately 20 min.
Dosage and administration

Induction of anaesthesia is achieved with an average dose of 2 mg kg$^{-1}$ i.v.; larger doses may be required in some patients, and smaller doses in the elderly or shocked patient. In all cases, the drug should be administered slowly. Additional doses of 1–1.5 mg kg$^{-1}$ are required every 5–10 min. Between 8 and 10 mg kg$^{-1}$ is used i.m. A dose of 0.25–0.5 mg kg$^{-1}$ or an infusion of 50µg kg$^{-1}$ min$^{-1}$ may be used to produce analgesia without loss of consciousness.

Adverse effects

- emergence delirium, nightmares and hallucinations
- hypertension and tachycardia – this may be harmful in previously hypertensive patients and in those with ischaemic heart disease
- prolonged recovery
- salivation – anticholinergic premedication is essential
- increased intracranial pressure
- allergic reactions – skin rashes have been reported.

Indications

The high-risk patient. Ketamine is useful in the shocked patient. Arterial pressure may decrease if hypovolaemia is present, and the drug must be given cautiously. These patients are usually heavily sedated in the postoperative period, and the risk of nightmares is therefore minimized.

Paediatric anaesthesia. Children undergoing minor surgery, investigations (e.g. cardiac catheterization), ophthalmic examinations or radiotherapy may be managed successfully with ketamine administered either i.m. or i.v.

Difficult locations. Ketamine has been used successfully at the site of accidents, and for analgesia and anaesthesia in casualties of war.

Analgesia and sedation. The analgesic action of ketamine may be used when wound dressings are changed, or while positioning patients with pain before performing regional anaesthesia (e.g. fractured neck of femur). Ketamine has been used to sedate asthmatic patients in the ICU.

Developing countries. Ketamine is used extensively in countries where anaesthetic equipment and trained staff are in short supply.

Absolute contraindications

- Airway obstruction – although the airway is maintained better with ketamine than with other agents, its patency cannot be guaranteed.
- Inhalational agents should be used for induction of anaesthesia if airway obstruction is anticipated.
- Raised intracranial pressure.

Precautions

Cardiovascular disease. Ketamine is unsuitable for patients with pre-existing hypertension, ischaemic heart disease or severe cardiac decompensation.

Repeated administration. Because of the prolonged recovery period, ketamine is not the most suitable drug for frequent procedures, e.g. prolonged courses of radiotherapy, as it disrupts sleep and eating patterns.

Visceral stimulation. Ketamine suppresses poorly the response to visceral stimulation; supplementation, e.g. with an opioid, is indicated if visceral stimulation is anticipated.

Outpatient anaesthesia. The prolonged recovery period and emergence phenomena make ketamine unsuitable for adult outpatients.

OTHER DRUGS

Opioids and benzodiazepines may also be used to induce general anaesthesia. However, very large doses are required, and recovery is prolonged. Their use is confined to specialist areas, e.g. cardiac anaesthesia. The pharmacology of these drugs is described in Chapters 5 and 7, respectively.

INDICATIONS FOR INTRAVENOUS MAINTENANCE OF ANAESTHESIA

There are several situations in which i.v. anaesthesia (IVA; the use of an i.v. anaesthetic to supplement nitrous oxide) or total i.v. anaesthesia (TIVA) may offer advantages over the traditional inhalational techniques. In the doses required to maintain clinical anaesthesia, i.v. agents cause minimal cardiovascular depression. In comparison with the most commonly used volatile anaesthetic agents, IVA with propofol (the only currently available i.v. anaesthetic with an appropriate pharmacokinetic profile) offers rapid recovery of consciousness and good recovery of psychomotor function, although the newer volatile anaesthetics desflurane and sevoflurane are also associated with rapid recovery and minimal hangover effects.
The use of TIVA allows a high inspired oxygen concentration in situations where hypoxaemia may otherwise occur, such as one-lung anaesthesia or in severely ill or traumatized patients, and has obvious advantages in procedures such as laryngoscopy or bronchoscopy, when delivery of inhaled anaesthetic agents to the lungs may be difficult. TIVA may also be used to provide anaesthesia in circumstances where there are clinical reasons to avoid nitrous oxide, such as middle-ear surgery, prolonged bowel surgery and in patients with raised intracranial pressure. There are few contraindications to the use of IVA, provided that the anaesthetist is aware of the wide variability in response (see below). For surgical anaesthesia, it is desirable either to use nitrous oxide supplemented by IVA or to infuse an opioid in addition to the i.v. anaesthetic.

PRINCIPLES OF IVA

The calibrated vaporizer allows the anaesthetist to establish stable conditions, usually with relatively few changes in delivered concentration of volatile anaesthetic agents during an operation. This is largely because the patient tends to come into equilibrium with the delivered concentration, irrespective of body size or physiological variations; the total dose of drug taken up by the body is variable, but is relatively unimportant, and is determined by the characteristics of the patient and the drug rather than by the anaesthetist. The task of achieving equilibrium with i.v. anaesthetic agents is more complex, as delivery must be matched to the size of the patient and also to the expected rates of distribution and metabolism of the drug. Conventional methods of delivering i.v. agents result in the total dose of drug being determined by the anaesthetist, and the concentration achieved in the brain depends on the volume and rate of distribution, the relative solubility of the agent in various tissues and the rate of elimination of the drug in the individual patient. Consequently, there is considerably more variability among patients in the infusion rate of an i.v. anaesthetic required to produce satisfactory anaesthesia than there is in the inspired concentration of an inhaled agent. There is concern among some anaesthetists that the difficulty in predicting the correct infusion rate for an individual patient may result in a higher risk of awareness in the paralysed patient, although the risks appear in practice to be similar, and related to inadvertent failure of delivery of the drug or the use of inappropriate infusion schemes rather than to an inherent flaw in the technique.

TECHNIQUES OF ADMINISTRATION

Intermittent injection

Although some anaesthetists are skilled in the delivery of i.v. anaesthetic agents by intermittent bolus injection, the plasma concentrations of drug and the anaesthetic effect fluctuate widely, and the technique is acceptable only for procedures of short duration in unparalysed patients.

Manual infusion techniques

The infusion rate required to achieve a predetermined concentration of an i.v. drug can be calculated if the clearance of the drug from plasma is known [infusion rate (µg min⁻¹) = steady-state plasma concentration (µg mL⁻¹) x clearance (mL min⁻¹)]. One of the difficulties is that clearance is variable, and it is possible only to estimate the value by using population kinetics; depending on the patient’s clearance in relation to the average, the actual plasma concentration achieved may be higher or lower than the intended concentration.

A fixed-rate infusion is inappropriate because the serum concentration of the drug increases only slowly, taking four to five times the elimination half-life of the drug to reach steady state (Fig. 3.4). A bolus injection followed by a continuous infusion results initially in achievement of an excessive concentration (with an increased incidence of side-effects), and this is followed by a prolonged dip below the intended plasma concentration (Fig. 3.5). In order to achieve a reasonably constant plasma concentration (other than in very long procedures), it is necessary to use a multistep infusion

![Fig. 3.4](image_url)

*Fig. 3.4* Average blood concentration during the first 2 h of a continuous infusion of propofol at a rate of 6 mg kg⁻¹ h⁻¹. Note that, even after 2 h, the equilibrium concentration of 3 µg mL⁻¹ has not been achieved.
regimen, a concept similar to that of overpressure for inhaled agents. A commonly used scheme for propofol is injection of a bolus dose of 1 mg kg\(^{-1}\) followed by infusion initially at a rate of 10 mg kg\(^{-1}\) h\(^{-1}\) for 10 min, then 8 mg kg\(^{-1}\) h\(^{-1}\) for the next 10 min, and a maintenance infusion rate of 6 mg kg\(^{-1}\) h\(^{-1}\) thereafter. This achieves, on average, a plasma concentration of propofol of 3 µg mL\(^{-1}\), and this is effective in achieving satisfactory anaesthesia in unparalysed patients who also receive nitrous oxide and fentanyl; higher infusion rates are required if nitrous oxide and fentanyl are not administered. These infusion rates must be regarded only as a guide and must be adjusted as necessary according to clinical signs of anaesthesia.

**Target-controlled infusion (TCI) techniques**

By programming a computer with appropriate pharmacokinetic data and equations, it is possible at frequent intervals (several times a minute) to calculate the appropriate infusion rate required to produce a preset target plasma concentration of drug. The drug is infused by a syringe driver. To produce a step increase in plasma concentration, the syringe driver infuses drug very rapidly (a slow bolus) and then delivers drug at a progressively decreasing infusion rate (Fig. 3.6). To decrease the plasma concentration, the syringe driver stops infusing until the computer calculates that the target concentration has been achieved, and then infuses drug at an appropriate rate to maintain a constant level. The anaesthetist is required only to enter the desired target concentration and to change it when clinically indicated, in the same way as a vaporizer might be manipulated according to clinical signs of anaesthesia.

The potential advantages of such a system are its simplicity, the rapidity with which plasma concentration can be changed (particularly upwards) and avoidance of the need for the anaesthetist to undertake any calculations (resulting in less potential for error). The actual concentration achieved may be >50% greater than or less than the predicted concentration, although this is not a major practical disadvantage provided that the anaesthetist adjusts the target concentration according to clinical signs relating to adequacy of anaesthesia, rather than assuming that a specific target concentration always results in the desired effect.

Using a TCI system in female patients, the target concentration of propofol required to prevent movement in response to surgical incision in 50% of subjects (the equivalent of minimum alveolar concentration; MAC) was 6 µg mL\(^{-1}\) when patients breathed oxygen, and 4.5 µg mL\(^{-1}\) when 67% nitrous oxide was administered simultaneously.

A TCI system for administration of propofol is available in many countries. The anaesthetist is required to input the weight and age of the patient, and then to select the desired target concentration. These devices can be used only with prefilled syringes, which contain an electronic tag that is recognized by the infusion pump. These TCI systems are
currently suitable for use only in patients over the age of 16 years. Target concentrations selected for elderly patients should be lower than those for younger adults, in order to minimize the risk of side-effects.

The TCI infusion pumps assume that the patient is conscious when the infusion is started. Consequently, it is inappropriate to connect and start a TCI system in a patient who is already unconscious, as this results in an initial overdose.

In adult patients under 55 years of age, anaesthesia may be induced usually with a target propofol concentration of 4–8 µg mL\(^{-1}\). An initial target concentration at the lower end of that range is suitable for premedicated patients. Induction time is usually between 1 and 2 min. The brain concentration of propofol increases more slowly than the blood concentration, and following induction it is usually appropriate to reduce the target concentration; target propofol concentrations in the range of 3–6 µg mL\(^{-1}\) usually maintain satisfactory anaesthesia in patients who are also receiving an analgesic drug.

Later versions of the TCI infusion pumps show the predicted brain concentration, which may be used as a guide to the timing of alterations in the blood target concentration.

Closed-loop systems

Target-controlled infusion systems may be used as part of a closed-loop system to control depth of anaesthesia. Because there is no method of measuring blood concentrations of i.v. anaesthetics on-line, it is necessary to use some type of monitor of depth of anaesthesia (such as the auditory evoked response; see Ch. 18) on the input side of the system.

ADVERSE REACTIONS TO INTRAVENOUS ANAESTHETIC AGENTS

These may take the form of pain on injection, venous thrombosis, involuntary muscle movement, hiccup, hypotension and postoperative delirium. All of these reactions may be modified by the anaesthetic technique.

Hypersensitivity reactions, which resemble the effects of histamine release, are more rare and less predictable. Other vasoactive agents may also be released. Reactions to i.v. anaesthetic agents are caused usually by one of the following mechanisms:

*Type I hypersensitivity response.* The drug interacts with specific immunoglobulin E (IgE) antibodies, which are often bound to the surface of mast cells; these become granulated and release histamine and other vasoactive amines.

*Classic complement-mediated reaction.* The classic complement pathway may be activated by type II (cell surface antigen) or type III (immune complex formation) hypersensitivity reactions. IgG or IgM antibodies are involved.

*Alternate complement pathway activation.* Preformed antibodies to an antigen are not necessary for activation of this pathway; these may therefore occur without prior exposure to the drug.

*Direct pharmacological effects of the drug.* These anaphylactoid reactions result from a direct effect on mast cells and basophils. There may be local cutaneous signs only. In more severe reactions, there are signs of systemic release of histamine.

Clinical features

In a severe hypersensitivity reaction, a flush may develop over the upper part of the body. There is usually hypotension, which may be profound. Cutaneous and glottic oedema may develop and may result in hypovolaemia because of loss of fluid from the circulation. Very severe bronchospasm may also occur, although it is a feature in less than 50% of reactions. Diarrhoea often occurs some hours after the initial reaction.

Predisposing factors

*Age.* In general, adverse reactions are less common in children than in adults.

*Pregnancy.* There is an increased incidence of adverse reactions in pregnancy.

*Gender.* Anaphylactic reactions are more common in women.

*Atopy.* There may be an increased incidence of type IV (delayed hypersensitivity) reactions in non-atopic individuals, and a higher incidence of type I reactions in those with a history of extrinsic asthma, hay fever or penicillin allergy.

*Previous exposure.* Previous exposure to the drug, or to a drug with similar constituents, exerts a much greater influence on the incidence of reactions than does a history of atopy.

*Solvents.* Cremophor EL, which was used as a solvent for several i.v. anaesthetic agents, was associated with a high incidence of hypersensitivity reactions.

Incidence

The incidences of hypersensitivity reactions associated with i.v. anaesthetic agents are shown in Table 3.6.
Treatment

This is summarized in Table 3.7. Appropriate investigations should be undertaken after recovery to identify the drug responsible for the reaction.

FURTHER READING

Sneyd J R 2004 Recent advances in intravenous anaesthesia. British Journal of Anaesthesia 93: 725–736

Table 3.6 Incidences of adverse reactions to intravenous anaesthetic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>1:14 000–1:20 000</td>
</tr>
<tr>
<td>Methohexital</td>
<td>1:1600–1:7000</td>
</tr>
<tr>
<td>Etomidate</td>
<td>1:450 000</td>
</tr>
<tr>
<td>Propofol</td>
<td>1:50 000–100 000 (estimated)</td>
</tr>
</tbody>
</table>

Table 3.7 Suggested management of suspected anaphylaxis during anaesthesia

**Aims**

- Correct arterial hypoxaemia
- Restore intravascular fluid volume
- Inhibit further release of chemical mediators

**Immediate management**

1. Stop administration of all agents likely to have caused the anaphylaxis
2. Call for help
3. Maintain airway, give 100% oxygen and lie patient supine with legs elevated
4. Give epinephrine (adrenaline). This may be given intramuscularly in a dose of 0.5–1 mg (0.5–1 mL of 1:1000) and may be repeated every 10 min according to the arterial pressure and pulse until improvement occurs
   Alternatively, 50–100 µg intravenously (0.5–1 mL of 1:10 000) over 1 min has been recommended for hypotension with titration of further doses as required
   *Never give undiluted epinephrine 1:1000 intravenously*
   In a patient with cardiovascular collapse, 0.5–1 mg (5–10 mL of 1:10 000) may be required intravenously in divided doses by titration. This should be given at a rate of 0.1 mg min⁻¹ stopping when a response has been obtained
   Paediatric doses of epinephrine depend on the age of the child. Intramuscular epinephrine 1:1000 should be administered as follows:
   - >12 years 500 µg i.m. (0.5 mL)
   - 6–12 years 250 µg i.m. (0.25 mL)
   - >6 months to 6 years 120 µg i.m. (0.12 mL)
   - <6 months 50 µg i.m. (0.05 mL)
5. Start rapid intravenous infusion of colloids or crystalloids. Adult patients may require 2–4 L of crystalloid

**Secondary management**

1. Give antihistamines (chlorpheniramine 10–20 mg by slow i.v. infusion)
2. Give corticosteroids (100–500 mg hydrocortisone slowly i.v.)
3. Bronchodilators may be required for persistent bronchospasm