CHAPTER 9

Intravenous Anesthetics

KEY CONCEPTS

1. Repetitive administration of barbiturates (eg, infusion of thiopental for "barbiturate coma" and brain protection) saturates the peripheral compartments, minimizing any effect of redistribution, and rendering the duration of action more dependent on elimination. This is an example of context sensitivity.
2. Barbiturates constrict the cerebral vasculature, causing a decrease in cerebral blood flow, cerebral blood volume, and intracranial pressure.
3. Although apnea may be relatively uncommon after benzodiazepine induction, even small intravenous doses of diazepam and midazolam have resulted in respiratory arrest.
4. In contrast to other anesthetic agents, ketamine increases arterial blood pressure, heart rate, and cardiac output, particularly after rapid bolus injections.
5. Induction doses of etomidate transiently inhibit enzymes involved in cortisol and aldosterone synthesis. Etomidate was often used in the past for ICU sedation before reports of its consistent ability to produce adrenocortical suppression in that circumstance appeared.
6. Propofol formulations can support the growth of bacteria, so sterile technique must be observed in preparation and handling. Propofol should be administered within 6 h of opening the ampule.

General anesthesia began with inhaled agents but now can be induced and maintained with drugs that enter the patient through a wide range of routes. Drug administration can be oral, rectal, transdermal, transmucosal, intramuscular, or intravenous for the purpose of producing or enhancing an anesthetic state. Preoperative sedation of adults is usually accomplished by way of oral or intravenous routes. Induction of general anesthesia in adults usually includes intravenous drug administration. Effective topical anesthesia with EMLA (eutectic mixture of local anesthetic) cream, LMX (plain lidocaine cream 4% and 5%), or 2% lidocaine jelly has increased the ease of intravenous inductions in children. Maintenance of general anesthesia is feasible with a total intravenous anesthesia (TIVA) technique. This chapter focuses on the intravenous agents used to produce hypnosis, including barbiturates, benzodiazepines, ketamine, etomidate, and propofol.

BARBITURATES

Mechanisms of Action

Barbiturates depress the reticular activating system in the brainstem, which controls multiple vital functions, including consciousness. In clinical concentrations, barbiturates more potently affect the function of nerve synapses than axons. Their primary

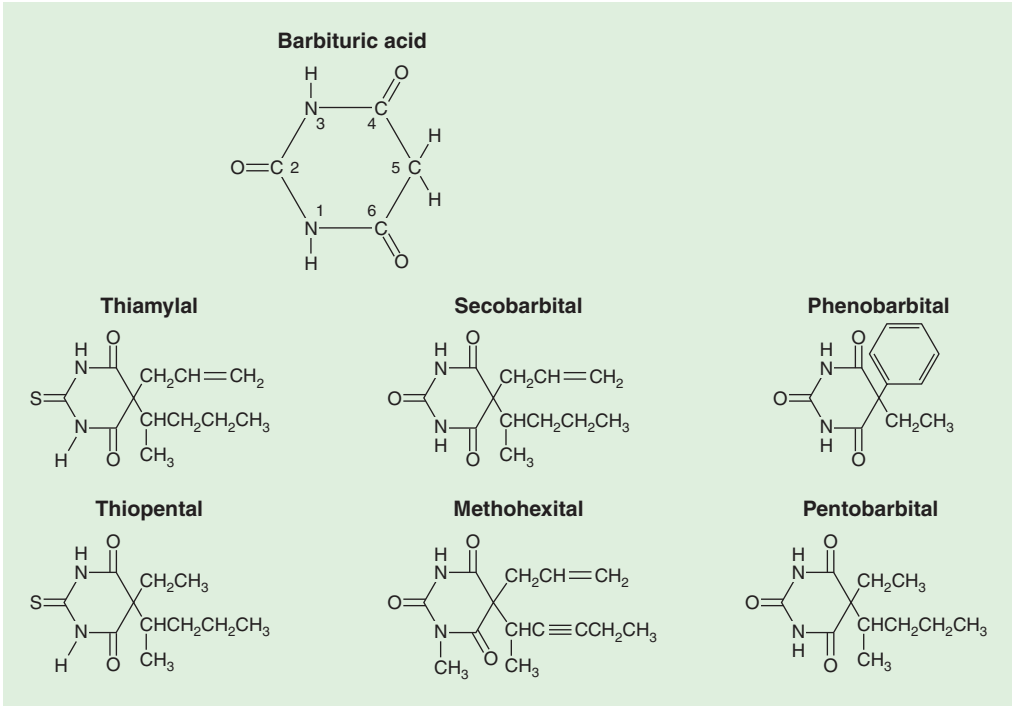

FIGURE 9–1 Barbiturates share the structure of barbituric acid and differ in the C_2, C_3, and N_1 substitutions.

mechanism of action is believed to be through binding to the γ-aminobutyric acid type A ($GABA_A$) receptor. Barbiturates potentiate the action of GABA in increasing the duration of openings of a chloride-specific ion channel.

Structure–Activity Relationships

Barbiturates are derived from barbituric acid (Figure 9–1). Substitution at carbon C_5 determines hypnotic potency and anticonvulsant activity. A long-branched chain conveys more potency than does a short straight chain. Likewise, the phenyl group in *pheno*barbital is anticonvulsive, whereas the methyl group in *metho*hexital is not. Replacing the oxygen at C_2 (*oxy*barbiturates) with a sulfur atom (*thio*-barbiturates) increases lipid solubility. As a result, thiopental and thiamylal have a greater potency, more rapid onset of action, and shorter durations of action (after a single "sleep dose") than pentobarbital. The sodium salts of the barbiturates are water soluble but markedly alkaline (pH of 2.5% thiopental >10) and relatively unstable (2-week shelf-life for 2.5% thiopental solution). Concentrations greater than recommended cause an unacceptable incidence of pain on injection and venous thrombosis.

Pharmacokinetics

A. Absorption

In clinical anesthesiology, thiopental, thiamylal, and methohexital were frequently administered intravenously for induction of general anesthesia in adults and children (prior to the introduction of propofol). Rectal thiopental or, more often, methohexital has been used for induction in children, and intramuscular (or oral) pentobarbital was often used in the past for premedication of all age groups.

B. Distribution

The duration of sleep doses of the highly lipid-soluble barbiturates (thiopental, thiamylal, and methohexital) is determined by redistribution, not by metabolism or elimination. For example, although thiopental is highly protein bound (80%), its great lipid solubility and high nonionized fraction (60%)

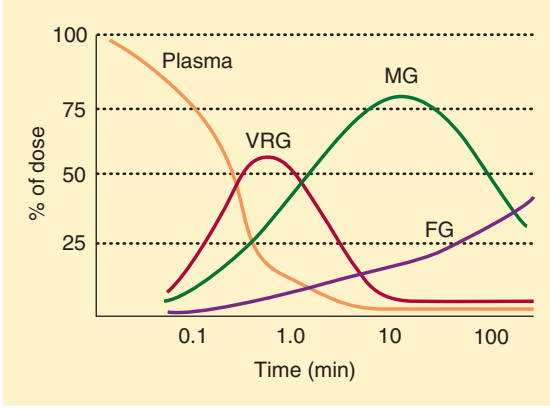

FIGURE 9–2 Distribution of thiopental from plasma to the vessel-rich group (VRG; brain, heart, liver, kidney, endocrine glands), to the muscle group (MG), and finally to the fat group (FG). (Modified and reproduced, with permission, from Price HL et al: The uptake of thiopental by body tissues and its relation to the duration of narcosis. Clin Pharmacol Ther 1960;1:16.)

account for rapid brain uptake (within 30 s). If the central compartment is contracted (eg, hypovolemic shock), if the serum albumin is low (eg, severe liver disease or malnutrition), or if the nonionized fraction is increased (eg, acidosis), larger brain and heart concentrations will be achieved for a given dose. Redistribution to the peripheral compartment—specifically, the muscle group—lowers plasma and brain concentration to 10% of peak levels within 20–30 min (Figure 9–2). This pharmacokinetic profile correlates with clinical experience—patients typically lose consciousness within 30 s and awaken within 20 min.

The minimal induction dose of thiopental will depend on body weight and age. Reduced induction doses are required for elderly patients primarily due to slower redistribution. In contrast to the rapid initial distribution half-life of a few minutes, elimination of thiopental is prolonged (elimination half-life ranges of 10–12 h). Thiamylal and methohexital have similar distribution patterns, whereas less lipid-soluble barbiturates have much longer distribution half-lives and durations of action after a sleep dose. Repetitive

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administration of barbiturates (eg, infusion of thiopental for "barbiturate coma" and brain protection) saturates the peripheral compartments, minimizing any effect of redistribution, and rendering the duration of action more dependent on elimination. This is an example of context sensitivity.

C. Biotransformation

Barbiturates are principally biotransformed via hepatic oxidation to inactive water-soluble metabolites. Because of greater hepatic extraction, methohexital is cleared by the liver more rapidly than thiopental. Although redistribution is responsible for the awakening from a single sleep dose of any of these lipid-soluble barbiturates, full recovery of psychomotor function is more rapid following methohexital due to its enhanced metabolism.

D. Excretion

Increased protein binding decreases barbiturate glomerular filtration, whereas increased lipid solubility tends to increase renal tubular reabsorption. Except for the less protein-bound and less lipid-soluble agents such as phenobarbital, renal excretion is limited to water-soluble end products of hepatic biotransformation. Methohexital is excreted in the feces.

Effects on Organ Systems

A. Cardiovascular

Intravenous bolus induction doses of barbiturates cause a decrease in blood pressure and an increase in heart rate. Hemodynamic responses to barbiturates are reduced by slower rates of induction. Depression of the medullary vasomotor center produces vasodilation of peripheral capacitance vessels, which increases peripheral pooling of blood, mimicking a reduced blood volume. Tachycardia following administration is probably due to a central vagolytic effect and reflex responses to decreases in blood pressure. Cardiac output is often maintained by an increased heart rate and increased myocardial contractility from compensatory baroreceptor reflexes. Sympathetically induced vasoconstriction of resistance vessels (particularly with intubation under light planes of general anesthesia) may actually increase peripheral vascular resistance. However, in situations where the baroreceptor response will be blunted or absent (eg, hypovolemia, congestive heart failure, β-adrenergic blockade), **cardiac output and arterial blood pressure may fall dramatically due**

to uncompensated peripheral pooling of blood and direct myocardial depression. Patients with poorly controlled hypertension are particularly prone to wide swings in blood pressure during anesthesia induction. The cardiovascular effects of barbiturates therefore vary markedly, depending on rate of administration, dose, volume status, baseline autonomic tone, and preexisting cardiovascular disease. A slow rate of injection and adequate preoperative hydration attenuates or eliminates these changes in most patients.

B. Respiratory

Barbiturates depress the medullary ventilatory center, decreasing the ventilatory response to hypercapnia and hypoxia. Deep barbiturate sedation often leads to upper airway obstruction; apnea often follows an induction dose. During awakening, tidal volume and respiratory rate are decreased following barbiturate induction. Barbiturates incompletely depress airway reflex responses to laryngoscopy and intubation, and airway instrumentation may lead to bronchospasm (in asthmatic patients) or laryngospasm in lightly anesthetized patients.

C. Cerebral

2 Barbiturates constrict the cerebral vasculature, causing a decrease in cerebral blood flow, cerebral blood volume, and intracranial pressure. Intracranial pressure decreases to a greater extent than arterial blood pressure, so cerebral perfusion pressure (CPP) usually increases. (CPP equals cerebral artery pressure minus the greater of jugular venous pressure or intracranial pressure.) Barbiturates induce a greater decline in cerebral oxygen consumption (up to 50% of normal) than in cerebral blood flow; therefore the decline in cerebral blood flow is not detrimental. Barbiturate-induced reductions in oxygen requirements and cerebral metabolic activity are mirrored by changes in the electroencephalogram (EEG), which progress from low-voltage fast activity with small doses to high-voltage slow activity, burst suppression, and electrical silence with larger doses. Barbiturates may protect the brain from transient episodes of focal ischemia (eg, cerebral embolism) but probably do not protect from global ischemia (eg, cardiac arrest). Abundant animal data document these effects but the clinical data are sparse and inconsistent. Furthermore, thiopental doses required to maintain EEG suppression (most often burst suppression or flat line) are associated with prolonged awakening, delayed extubation, and the need for inotropic support.

The degree of central nervous system depression induced by barbiturates ranges from mild sedation to unconsciousness, depending on the dose administered (Table 9–1). Some patients relate a taste sensation of garlic, onions, or pizza during induction with thiopental. Barbiturates do not impair the perception of pain. In fact, they sometimes appear to lower the pain threshold. Small doses occasionally cause a state of excitement and disorientation that can be disconcerting when sedation is the objective. Barbiturates do not produce

TABLE 9–1 Uses and dosages of common barbiturates.

Agent	Use	Route[1]	Concentration (%)	Dose (mg/kg)
Thiopental, thiamylal	Induction	IV	2.5	3–6
Methohexital	Induction Sedation Induction	IV IV Rectal (children)	1 1 10	1–2 0.2–0.4 25
Secobarbital, pentobarbital	Premedication	Oral IM Rectal suppository	5	2–4[2] 2–4[2] 3

[1]IV, intravenous; IM, intramuscular.

[2]Maximum dose is 150 mg.

muscle relaxation, and some induce involuntary skeletal muscle contractions (eg, methohexital). Relatively small doses of thiopental (50–100 mg intravenously) rapidly (but temporarily) control most grand mal seizures. Unfortunately, acute tolerance and physiological dependence on the sedative effect of barbiturates develop quickly.

D. Renal

Barbiturates reduce renal blood flow and glomerular filtration rate in proportion to the fall in blood pressure.

E. Hepatic

Hepatic blood flow is decreased. Chronic exposure to barbiturates has opposing effects on drug biotransformation. Induction of hepatic enzymes increases the rate of metabolism of some drugs, whereas binding of barbiturates to the cytochrome P-450 enzyme system interferes with the biotransformation of other drugs (eg, tricyclic antidepressants). Barbiturates promote aminolevulinic acid synthetase, which stimulates the formation of **porphyrin** (an intermediary in heme synthesis). This may precipitate acute intermittent porphyria or variegate porphyria in susceptible individuals.

F. Immunological

Anaphylactic or anaphylactoid allergic reactions are rare. Sulfur-containing thiobarbiturates evoke mast cell histamine release in vitro, whereas oxybarbiturates do not. For this reason, some anesthesiologists prefer induction agents other than thiopental or thiamylal in asthmatic or atopic patients, but the evidence for this choice is sparse. There is no question that airway instrumentation with light anesthesia is troublesome in patients with reactive airways.

Drug Interactions

Contrast media, sulfonamides, and other drugs that occupy the same protein-binding sites as thiopental may displace the barbiturate, increasing the amount of free drug available and potentiating the organ system effects of a given dose.

Ethanol, opioids, antihistamines, and other central nervous system depressants potentiate the sedative effects of barbiturates. The common clinical impression that chronic alcohol abuse is associated with increased thiopental requirements during induction lacks scientific proof.

BENZODIAZEPINES

Mechanisms of Action

Benzodiazepines bind the same set of receptors in the central nervous system as barbiturates but bind to a different site on the receptors. Benzodiazepine binding to the $GABA_A$ receptor increases the frequency of openings of the associated chloride ion channel. For example, benzodiazepine-receptor binding facilitates binding of GABA to its receptor. **Flumazenil** (an imidazobenzodiazepine) is a specific benzodiazepine–receptor antagonist that effectively reverses most of the central nervous system effects of benzodiazepines (see Chapter 17).

Structure–Activity Relationships

The chemical structure of benzodiazepines includes a benzene ring and a seven-member diazepine ring (Figure 9–3). Substitutions at various positions on these rings affect potency and biotransformation. The imidazole ring of midazolam contributes to its water solubility at low pH. Diazepam and lorazepam are insoluble in water so parenteral preparations contain propylene glycol, which can produce venous irritation.

Pharmacokinetics

A. Absorption

Benzodiazepines are commonly administered orally, intramuscularly, and intravenously to provide sedation or, less commonly, to induce general anesthesia (Table 9–2). Diazepam and lorazepam are well absorbed from the gastrointestinal tract, with peak plasma levels usually achieved in 1 and 2 h, respectively. Oral midazolam has not been approved by the U.S. Food and Drug Administration, nevertheless this route of administration has been popular for pediatric premedication. Likewise, intranasal (0.2–0.3 mg/kg), buccal (0.07 mg/kg), and sublingual (0.1 mg/kg) midazolam provide effective preoperative sedation.

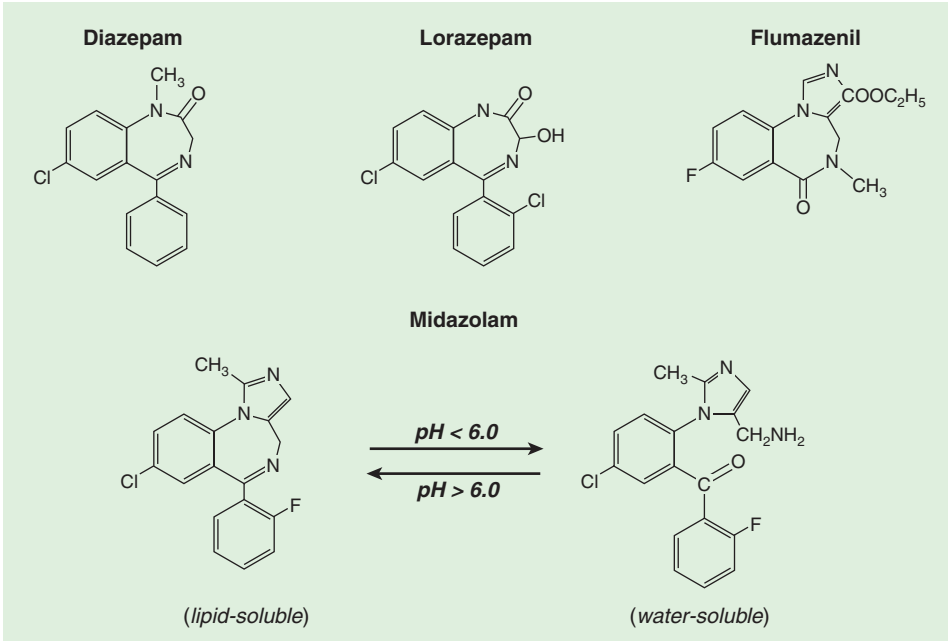

FIGURE 9–3 The structures of commonly used benzodiazepines and their antagonist, flumazenil, share a seven-member diazepine ring. (Modified and reproduced, with permission, from White PF: Pharmacologic and clinical aspects of preoperative medication. Anesth Analg 1986;65:963. With permission from the International Anesthesia Research Society.)

Intramuscular injections of diazepam are painful and unreliably absorbed. In contrast, midazolam and lorazepam are well absorbed after intramuscular injection, with peak levels achieved in 30 and 90 min, respectively. Induction of general anesthesia with midazolam is convenient only with intravenous administration.

TABLE 9–2 Uses and doses of commonly used benzodiazepines.

Agent	Use	Route[1]	Dose (mg/kg)
Diazepam	Premedication Sedation	Oral IV	0.2–0.5[2] 0.04–0.2
Midazolam	Premedication Sedation Induction	IM IV IV	0.07–0.15 0.01–0.1 0.1–0.4
Lorazepam	Premedication	Oral	0.05

[1]IV, intravenous; IM, intramuscular.

[2]Maximum dose is 15 mg.

B. Distribution

Diazepam is relatively lipid soluble and readily penetrates the blood–brain barrier. Although midazolam is water soluble at reduced pH, its imidazole ring closes at physiological pH, increasing its lipid solubility (see Figure 9–3). The moderate lipid solubility of lorazepam accounts for its slower brain uptake and onset of action. Redistribution is fairly rapid for the benzodiazepines (the initial distribution half-life is 3–10 min) and, like the barbiturates, is responsible for awakening. Although midazolam has been used as an induction agent, neither midazolam nor any other of the benzodiazepines can match the rapid onset and short duration of action of propofol or even thiopental. All three benzodiazepines are highly protein bound (90–98%).

C. Biotransformation

The benzodiazepines rely on the liver for biotransformation into water-soluble glucuronidated end products. The phase I metabolites of diazepam are pharmacologically active.

Slow hepatic extraction and a large volume of distribution (V_d) result in a long elimination half-life for diazepam (30 h). Although lorazepam also has a low hepatic extraction ratio, its lower lipid solubility limits its V_d, resulting in a shorter elimination half-life (15 h). Nonetheless, the clinical duration of lorazepam is often quite prolonged due to increased receptor affinity. These differences between lorazepam and diazepam illustrate the low utility of individual pharmacokinetic half-lives in guiding clinical practice. Midazolam shares diazepam's V_d, but its elimination half-life (2 h) is the shortest of the group because of its increased hepatic extraction ratio.

D. Excretion

The metabolites of benzodiazepine biotransformation are excreted chiefly in the urine. Enterohepatic circulation produces a secondary peak in diazepam plasma concentration 6–12 h following administration. Kidney failure may lead to prolonged sedation in patients receiving larger doses of midazolam due to the accumulation of a conjugated metabolite (α-hydroxymidazolam).

Effects on Organ Systems

A. Cardiovascular

The benzodiazepines display minimal cardiovascular depressant effects even at general anesthetic doses, except when they are coadministered with opioids (these agents interact to produce myocardial depression and arterial hypotension). Benzodiazepines given alone decrease arterial blood pressure, cardiac output, and peripheral vascular resistance slightly, and sometimes increase heart rate. Intravenous midazolam tends to reduce blood pressure and peripheral vascular resistance more than diazepam. Changes in heart rate variability during midazolam sedation suggest decreased vagal tone (ie, drug-induced vagolysis).

B. Respiratory

Benzodiazepines depress the ventilatory response to CO_2. This depression is usually insignificant unless the drugs are administered intravenously or in association with other respiratory depressants. Although apnea may be relatively uncommon after benzodiazepine induction, even small intravenous doses of diazepam and midazolam have resulted in respiratory arrest. The steep dose–response curve, slightly prolonged onset (compared with propofol or thiopental), and potency of midazolam necessitate careful titration to avoid overdosage and apnea. Ventilation must be monitored in all patients receiving intravenous benzodiazepines, and resuscitation equipment must be immediately available.

C. Cerebral

Benzodiazepines reduce cerebral oxygen consumption, cerebral blood flow, and intracranial pressure but not to the extent the barbiturates do. They are effective in preventing and controlling grand mal seizures. Oral sedative doses often produce anterograde amnesia, a useful premedication property. The mild muscle-relaxing property of these drugs is mediated at the spinal cord level, not at the neuromuscular junction. The antianxiety, amnestic, and sedative effects seen at lower doses progress to stupor and unconsciousness at induction doses. Compared with propofol or thiopental, induction with benzodiazepines is associated with a slower rate of loss of consciousness and a longer recovery. Benzodiazepines have no direct analgesic properties.

Drug Interactions

Cimetidine binds to cytochrome P-450 and reduces the metabolism of diazepam. Erythromycin inhibits its metabolism of midazolam and causes a two- to threefold prolongation and intensification of its effects. Heparin displaces diazepam from protein-binding sites and increases the free drug concentration.

As previously mentioned, the combination of opioids and benzodiazepines markedly reduces arterial blood pressure and peripheral vascular resistance. This synergistic interaction has often been observed in patients with ischemic or valvular heart disease who often receive benzodiazepines for premedication and during induction of anesthesia with opioids.

Benzodiazepines reduce the minimum alveolar concentration of volatile anesthetics as much as 30%.

Ethanol, barbiturates, and other central nervous system depressants potentiate the sedative effects of the benzodiazepines.

KETAMINE

Mechanisms of Action

Ketamine has multiple effects throughout the central nervous system, inhibiting polysynaptic reflexes in the spinal cord as well as excitatory neurotransmitter effects in selected areas of the brain. In contrast to the depression of the reticular activating system induced by the barbiturates, ketamine functionally "dissociates" the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with the awareness of sensation). Clinically, this state of dissociative anesthesia may cause the patient to appear conscious (eg, eye opening, swallowing, muscle contracture) but unable to process or respond to sensory input. Ketamine has been demonstrated to be an *N*-methyl-D-aspartate (NMDA) receptor (a subtype of the glutamate receptor) antagonist.

Structure–Activity Relationships

Ketamine (Figure 9–4) is a structural analogue of phencyclidine (an anesthetic that has been used in veterinary medicine, and a drug of abuse). It is one-tenth as potent, yet retains many of phencyclidine's psychotomimetic effects. Ketamine is used for intravenous induction of anesthesia, particularly in settings where its tendency to produce sympathetic stimulation are useful (hypovolemia, trauma). When intravenous access is lacking, ketamine is useful for intramuscular induction of general anesthesia in children and uncooperative adults. Ketamine can be combined with other agents (eg, propofol or midazolam) in small bolus doses or infusions for deep conscious sedation during nerve blocks, endoscopy, etc. Even subanesthetic doses of ketamine may cause hallucinogenic effects but usually do not do so in clinical practice, where many patients will have received at least a small dose of midazolam (or a related agent) for amnesia and sedation. The increased anesthetic potency and decreased psychotomimetic side effects of one isomer (S[+] versus R[–]) are the result of stereospecific receptors. The single S(+) stereoisomer preparation is not available in the United States (but widely available throughout the world), and it has considerably greater affinity than the racemic mixture for the NMDA receptor as well as several-fold greater potency as a general anesthetic.

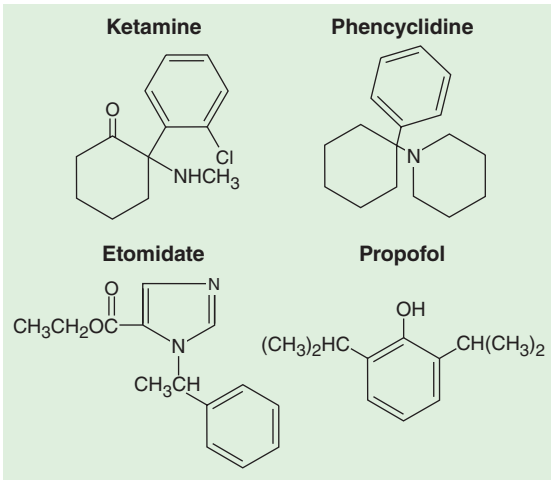

FIGURE 9–4 The structures of ketamine, etomidate, and propofol. Note the similarities between ketamine and phencyclidine.

Pharmacokinetics

A. Absorption

Ketamine has been administered orally, nasally, rectally, subcutaneously, and epidurally, but in usual clinical practice it is given intravenously or intramuscularly (Table 9–3). Peak plasma levels are usually achieved within 10–15 min after intramuscular injection.

B. Distribution

Ketamine is more lipid soluble and less protein bound than thiopental. These characteristics, along with ketamine-induced increase in cerebral blood flow and cardiac output, lead to rapid brain uptake and subsequent redistribution (the distribution half-life is 10–15 min). Awakening is due to redistribution from brain to peripheral compartments.

C. Biotransformation

Ketamine is biotransformed in the liver to several metabolites, one of which (norketamine) retains

TABLE 9–3 Uses and doses of ketamine, etomidate, and propofol.

Agent	Use	Route[1]	Dose
Ketamine	Induction	IV	1–2 mg/kg
		IM	3–5 mg/kg
	Sedation[2]	IV	2.5–15 mcg/kg/min
Etomidate	Induction	IV	0.2–0.5 mg/kg
Propofol	Induction	IV	1–2.5 mg/kg
	Maintenance infusion	IV	50–200 mcg/kg/min
	Sedation infusion	IV	25–100 mcg/kg/min

[1]IV, intravenous; IM, intramuscular.

[2]Almost always in combination with propofol.

anesthetic activity. Induction of hepatic enzymes only partially explains the tolerance that patients who receive multiple doses of ketamine will develop. Extensive hepatic uptake (hepatic extraction ratio of 0.9) explains ketamine's relatively short elimination half-life (2 h).

D. Excretion

End products of ketamine biotransformation are excreted renally.

Effects on Organ Systems

A. Cardiovascular

4 In contrast to other anesthetic agents, ketamine increases arterial blood pressure, heart rate, and cardiac output (Table 9–4), particularly after rapid bolus injections. These indirect cardiovascular effects are due to central stimulation of the sympathetic nervous system and inhibition of the reuptake of norepinephrine after release at nerve terminals. Accompanying these changes are increases in pulmonary artery pressure and myocardial work. For these reasons, large bolus injections of ketamine should be administered cautiously in patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, or arterial aneurysms. The **direct myocardial depressant** effects of large doses of ketamine, probably due to inhibition of calcium transients, are unmasked by sympathetic blockade (eg, spinal cord transection) or exhaustion of catecholamine stores (eg, severe end-stage shock). On the other hand, ketamine's **indirect stimulatory effects** may be beneficial to patients with acute shock.

B. Respiratory

Ventilatory drive is minimally affected by induction doses of ketamine, although rapid intravenous bolus

TABLE 9–4 Summary of nonvolatile anesthetic effects on organ systems.[1]

	Cardiovascular		Respiratory		Cerebral		
Agent	HR	MAP	Vent	B'dil	CBF	$CMRO_2$	ICP
Barbiturates							
Thiopental	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Thiamylal	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Methohexital	↑↑	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Benzodiazepines							
Diazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Lorazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Midazolam	↑	↓↓	↓↓	0	↓↓	↓↓	↓↓
Ketamine	↑↑	↑↑	↓	↑↑↑	↑↑[2]	↑	↑↑[2]
Etomidate	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Propofol	0	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓

[1]HR, heart rate; MAP, mean arterial pressure; Vent, ventilatory drive; B'dil, bronchodilation; CBF, cerebral blood flow; $CMRO_2$, cerebral oxygen consumption; ICP, intracranial pressure; 0, no effect; 0/↑, no change or mild increase; ↓, decrease (mild, moderate, marked); ↑, increase (mild, moderate, marked).

[2]Minimal change in CBF and ICP when coadministered with other agents (see text).

administration or combinations of ketamine with opioids occasionally produce apnea. Racemic ketamine is a potent bronchodilator, making it a good induction agent for asthmatic patients; however, S(+) ketamine produces minimal bronchodilation. Upper airway reflexes remain largely intact, but partial airway obstruction may occur, and patients at increased risk for aspiration pneumonia ("full stomachs") should be intubated during ketamine general anesthesia (see Case Discussion, Chapter 17). The increased salivation associated with ketamine can be attenuated by premedication with an anticholinergic agent such as glycopyrrolate

C. Cerebral

The received dogma about ketamine is that it increases cerebral oxygen consumption, cerebral blood flow, and intracranial pressure. These effects would seem to preclude its use in patients with space-occupying intracranial lesions such as occur with head trauma; however, recent publications offer convincing evidence that when combined with a benzodiazepine (or another agent acting on the same GABA receptor system) and controlled ventilation, but not with nitrous oxide, ketamine is *not* associated with increased intracranial pressure. Myoclonic activity is associated with increased subcortical electrical activity, which is not apparent on surface EEG. Undesirable psychotomimetic side effects (eg, disturbing dreams and delirium) during emergence and recovery are less common in children and in patients premedicated with benzodiazepines or those in whom ketamine is combined with propofol in a TIVA technique. Of the nonvolatile agents, ketamine comes closest to being a "complete" anesthetic as it induces analgesia, amnesia, and unconsciousness.

Drug Interactions

Ketamine interacts synergistically (more than additive) with volatile anesthetics but in an additive way with propofol, benzodiazepines, and other GABA-receptor–mediated agents. In animal experiments nondepolarizing neuromuscular blocking agents are minimally potentiated by ketamine (see Chapter 11). Diazepam and midazolam attenuate ketamine's cardiostimulatory effects and diazepam prolongs ketamine's elimination half-life.

α-Adrenergic and β-adrenergic antagonists (and other agents and techniques that diminish sympathetic stimulation) unmask the direct myocardial depressant effects of ketamine, which are normally overwhelmed by sympathetic stimulation. Concurrent infusion of ketamine and propofol, often in a fixed infusion rate ratio of 1:10, has achieved great popularity for sedation with local and regional anesthesia, particularly in office-based settings.

ETOMIDATE

Mechanisms of Action

Etomidate depresses the reticular activating system and mimics the inhibitory effects of GABA. Specifically, etomidate—particularly the R(+) isomer—appears to bind to a subunit of the $GABA_A$ receptor, increasing the receptor's affinity for GABA. Unlike barbiturates, etomidate may have disinhibitory effects on the parts of the nervous system that control extrapyramidal motor activity. This disinhibition offers a potential explanation for the 30–60% incidence of myoclonus with etomidate induction of anesthesia.

Structure–Activity Relationships

Etomidate contains a carboxylated imidazole and is structurally unrelated to other anesthetic agents (see Figure 9–4). The imidazole ring provides water solubility in acidic solutions and lipid solubility at physiological pH. Therefore etomidate is dissolved in propylene glycol for injection. This solution often causes pain on injection that can be lessened by a prior intravenous injection of lidocaine.

Pharmacokinetics

A. Absorption

Etomidate is available only for intravenous administration and is used primarily for induction of general anesthesia (see Table 9–3). It is sometimes used for brief production of deep (unconscious) sedation such as prior to placement of retrobulbar blocks.

B. Distribution

Although it is highly protein bound, etomidate is characterized by a very rapid onset of action due to its great lipid solubility and large nonionized fraction

at physiological pH. Redistribution is responsible for decreasing the plasma concentration to awakening levels. Etomidate plasma kinetics are well explained by a two-compartment model.

C. Biotransformation

Hepatic microsomal enzymes and plasma esterases rapidly hydrolyze etomidate to an inactive metabolite.

D. Excretion

The end products of etomidate hydrolysis are primarily excreted in the urine.

Effects on Organ Systems

A. Cardiovascular

Etomidate has minimal effects on the cardiovascular system. A mild reduction in peripheral vascular resistance is responsible for a slight decline in arterial blood pressure. Myocardial contractility and cardiac output are usually unchanged. Etomidate does not release histamine. However, etomidate by itself, even in large doses, produces relatively light anesthesia for laryngoscopy, and marked increases in heart rate and blood pressure may be recorded when etomidate provides the only anesthetic depth for intubation.

B. Respiratory

Ventilation is affected less with etomidate than with barbiturates or benzodiazepines. Even induction doses usually do not result in apnea unless opioids have also been administered.

C. Cerebral

Etomidate decreases cerebral metabolic rate, cerebral blood flow, and intracranial pressure. Because of minimal cardiovascular effects, CPP is well maintained. Although changes on EEG resemble those associated with barbiturates, etomidate increases the amplitude of somatosensory evoked potentials. Postoperative nausea and vomiting are more common following etomidate than following propofol or barbiturate induction. Etomidate lacks analgesic properties.

D. Endocrine

5 Induction doses of etomidate transiently inhibit enzymes involved in cortisol and aldosterone synthesis. It was used in the past for sedation in the intensive care unit (ICU) before reports of its consistent ability to produce adrenocortical suppression in that circumstance appeared. Long-term infusion and **adrenocortical suppression** were associated with an increased mortality rate in critically ill (particularly septic) patients.

Drug Interactions

Fentanyl increases the plasma level and prolongs the elimination half-life of etomidate. Opioids decrease the myoclonus characteristic of an etomidate induction.

PROPOFOL

Mechanisms of Action

Propofol induction of general anesthesia may involve facilitation of inhibitory neurotransmission mediated by $GABA_A$ receptor binding. Propofol allosterically increases binding affinity of GABA for the $GABA_A$ receptor. This receptor, as previously noted, is coupled to a chloride channel, and activation of the receptor leads to hyperpolarization of the nerve membrane. Propofol (like most general anesthetics) binds multiple ion channels and receptors. Propofol actions are not reversed by the specific benzodiazepine antagonist flumazenil.

Structure–Activity Relationships

Propofol consists of a phenol ring substituted with two isopropyl groups (see Figure 9–4). Propofol is not water soluble, but a 1% aqueous solution (10 mg/mL) is available for intravenous administration as an oil-in-water emulsion containing soybean oil, glycerol, and egg lecithin. A history of egg allergy does not necessarily contraindicate the use of propofol because most egg allergies involve a reaction to egg white (egg albumin), whereas egg lecithin is extracted from egg yolk. This formulation will often cause pain during injection that can be decreased by prior injection of lidocaine or less effectively by mixing lidocaine with propofol prior to injection (2 mL of 1% lidocaine in 18 mL propofol). 6 Propofol formulations can support the growth of bacteria, so sterile technique must be observed in preparation and handling. Propofol should be administered within 6 h of opening the

ampule. Sepsis and death have been linked to contaminated propofol preparations. Current formulations of propofol contain 0.005% disodium edetate or 0.025% sodium metabisulfite to help retard the rate of growth of microorganisms; however, these additives do not render the product "antimicrobially preserved" under United States Pharmacopeia standards.

Pharmacokinetics

A. Absorption

Propofol is available only for intravenous administration for the induction of general anesthesia and for moderate to deep sedation (see Table 9–3).

B. Distribution

Propofol has a rapid onset of action. Awakening from a single bolus dose is also rapid due to a very short initial distribution half-life (2–8 min). Most investigators believe that recovery from propofol is more rapid and is accompanied by less "hangover" than recovery from methohexital, thiopental, ketamine, or etomidate. This makes it a good agent for outpatient anesthesia. A smaller induction dose is recommended in elderly patients because of their smaller V_d. Age is also a key factor determining required propofol infusion rates for TIVA. In countries other than the United States, a device called the Diprifusor is often used to provide target (concentration) controlled infusion of propofol. The user must enter the patient's age and weight and the desired target concentration. The device uses these data, a microcomputer, and standard pharmacokinetic parameters to continuously adjust the infusion rate.

C. Biotransformation

The clearance of propofol exceeds hepatic blood flow, implying the existence of extrahepatic metabolism. This exceptionally high clearance rate probably contributes to relatively rapid recovery after continuous infusions. Conjugation in the liver results in inactive metabolites that are eliminated by renal clearance. The pharmacokinetics of propofol do not appear to be affected by obesity, cirrhosis, or kidney failure. Use of propofol infusion for long-term sedation of children who are critically ill or young adult neurosurgical patients has been associated with sporadic cases of lipemia, metabolic acidosis, and death, the so-termed *propofol infusion syndrome*.

D. Excretion

Although metabolites of propofol are primarily excreted in the urine, chronic kidney failure does not affect clearance of the parent drug.

Effects on Organ Systems

A. Cardiovascular

The major cardiovascular effect of propofol is a decrease in arterial blood pressure due to a drop in systemic vascular resistance (inhibition of sympathetic vasoconstrictor activity), preload, and cardiac contractility. Hypotension following induction is usually reversed by the stimulation accompanying laryngoscopy and intubation. Factors associated with propofol-induced hypotension include large doses, rapid injection, and old age. Propofol markedly impairs the normal arterial baroreflex response to hypotension. Rarely, a marked drop in preload may lead to a vagally mediated reflex bradycardia. Changes in heart rate and cardiac output are usually transient and insignificant in healthy patients but may be severe in patients at the extremes of age, those receiving β-adrenergic blockers, or those with impaired ventricular function. Although myocardial oxygen consumption and coronary blood flow usually decrease comparably, coronary sinus lactate production increases in some patients, indicating some mismatch between myocardial oxygen supply and demand.

B. Respiratory

Propofol is a profound respiratory depressant that usually causes apnea following an induction dose. Even when used for conscious sedation in subanesthetic doses, propofol inhibits hypoxic ventilatory drive and depresses the normal response to hypercarbia. As a result, only properly educated and qualified personnel should administer propofol for sedation. Propofol-induced depression of upper airway reflexes exceeds that of thiopental, allowing intubation, endoscopy, or laryngeal mask placement in the absence of neuromuscular blockade. Although propofol can cause histamine release, induction with propofol is accompanied by a lower incidence of

wheezing in asthmatic and nonasthmatic patients compared with barbiturates or etomidate.

C. Cerebral

Propofol decreases cerebral blood flow and intracranial pressure. In patients with elevated intracranial pressure, propofol can cause a critical reduction in CPP (<50 mm Hg) unless steps are taken to support mean arterial blood pressure. Propofol and thiopental probably provide a similar degree of cerebral protection during experimental focal ischemia. Unique to propofol are its antipruritic properties. Its antiemetic effects (requiring a blood propofol concentration of 200 ng/mL) provide yet another reason for it to be a preferred drug for outpatient anesthesia. Induction is occasionally accompanied by excitatory phenomena such as muscle twitching, spontaneous movement, opisthotonus, or hiccupping. Although these reactions may occasionally mimic tonic–clonic seizures, propofol has anticonvulsant properties and has been used successfully to terminate status epilepticus. Propofol may be safely administered to epileptic patients. Propofol decreases intraocular pressure. Tolerance does not develop after long-term propofol infusions. Propofol is an uncommon agent of physical dependence or addiction; however, both anesthesia personnel and medically untrained individuals have died while using propofol inappropriately to induce sleep in nonsurgical settings.

Drug Interactions

Fentanyl and alfentanil concentrations may be increased with concomitant administration of propofol. Many clinicians administer a small amount of midazolam (eg, 30 mcg/kg) prior to induction with propofol; midazolam can reduce the required propofol dose by more than 10%.

FOSPROPOFOL

Fospropofol is a water-soluble prodrug that is metabolized in vivo to propofol, phosphate, and formaldehyde. It has been released in the United States and other countries based on studies showing that it produces more complete amnesia and better conscious sedation for endoscopy than midazolam plus fentanyl. It has a slower onset and slower recovery than propofol, offering little reason for anesthesiologists to use fospropofol in place of propofol. The place (if any) of fospropofol relative to other competing agents has not yet been established in clinical practice.

CASE DISCUSSION

Premedication of the Surgical Patient

An extremely anxious 17-year-old woman presents for dilation and curettage. She demands to be asleep before going to the operating room and does not want to remember anything.

What are the goals of administering preoperative medication?

Anxiety is a normal response to impending surgery. Diminishing anxiety is usually the major goal of preoperative medication. For many patients, the preoperative interview with the anesthesiologist allays fears more effectively than sedative drugs. Preoperative medication may also provide relief of preoperative pain or perioperative amnesia.

There may also be specific medical indications for preoperative medication: prophylaxis against postoperative nausea and vomiting (5-HT_3s) and against aspiration pneumonia (eg, antacids), prevention of allergic reactions (eg, antihistamines), or decreasing upper airway secretions (eg, anticholinergics). The goals of preoperative medication depend on many factors, including the health and emotional status of the patient, the proposed surgical procedure, and the anesthetic plan. For this reason, the choice of anesthetic premedication must be individualized and must follow a thorough preoperative evaluation.

Do all patients require preoperative medication?

No—customary levels of preoperative anxiety do not harm most patients. Some patients dread intramuscular injections, and others find altered states of consciousness more unpleasant than nervousness. If the surgical procedure is brief, the effects of some sedatives may extend into the postoperative period and prolong recovery time. This is particularly troublesome for patients undergoing

ambulatory surgery. Specific contraindications for sedative premedication include severe lung disease, hypovolemia, impending airway obstruction, increased intracranial pressure, and depressed baseline mental status. Premedication with sedative drugs should never be given before informed consent has been obtained.

Which patients are most likely to benefit from preoperative medication?

Some patients are quite anxious despite the preoperative interview. Separation of young children from their parents is often a traumatic ordeal, particularly if they have endured multiple prior surgeries. Medical conditions such as coronary artery disease or hypertension may be aggravated by psychological stress.

How does preoperative medication influence the induction of general anesthesia?

Some medications often given preoperatively (eg, opioids) decrease anesthetic requirements and can smooth induction. However, intravenous administration of these medications just prior to induction is a more reliable method of achieving the same benefits.

What governs the choice among the preoperative medications commonly administered?

After the goals of premedication have been determined, the clinical effects of the agents dictate choice. For instance, in a patient experiencing preoperative pain from a femoral fracture, the analgesic effects of an opioid (eg, fentanyl, morphine, hydromorphone) will decrease the discomfort associated with transportation to the operating room and positioning on the operating room table. On the other hand, respiratory depression, orthostatic hypotension, and nausea and vomiting may result from opioid premedication.

Benzodiazepines relieve anxiety, often provide amnesia, and are relatively free of side effects; however, they are not analgesics. Diazepam and lorazepam are available orally. Intramuscular midazolam has a rapid onset (30 min) and short duration (90 min), but intravenous midazolam has an even better pharmacokinetic profile.

Which factors must be considered in selecting the anesthetic premedication for this patient?

First, it must be made clear to the patient that in most centers, lack of necessary equipment and concern for patient safety preclude anesthesia being induced in the preoperative holding room. Long-acting agents such as morphine or lorazepam are poor choices for an outpatient procedure. Diazepam can also affect mental function for several hours. One alternative is to establish an intravenous line in the preoperative holding area and titrate small doses of midazolam using slurred speech as an end point. At that time, the patient can be taken to the operating room. Vital signs—particularly respiratory rate—must be continuously monitored.

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