CHAPTER 9

Intravenous Anesthetics

KEY CONCEPTS

1. Repetitive administration of highly lipid-soluble 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 these agents 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. When used for sedation in the intensive care unit, etomidate produced adrenocortical suppression.
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 inhalation of ether, nitrous oxide, or chloroform, but in current practice, anesthesia and sedation can be induced and maintained with drugs that enter the patient through a wide range of routes. Preoperative or procedural sedation is usually accomplished by way of oral or intravenous routes. Induction of general anesthesia is typically accomplished by inhalation or intravenous drug administration. Alternatively, general anesthesia can be induced and maintained with intramuscular injection of ketamine. General anesthesia is typically maintained with a total intravenous anesthesia (TIVA) technique, an inhalation technique, or a combination of

the two. This chapter focuses on the injectable agents used to produce narcosis (sleep), including barbiturates, benzodiazepines, ketamine, etomidate, propofol, and dexmedetomidine.

BARBITURATES

At one time, nearly every general anesthetic in adults was induced with a barbiturate. These agents were also widely used for control of seizures, anxiolysis, and procedural sedation and as sleep-inducing agents. They are now much less widely used in anesthesia.

Mechanisms of Action

Barbiturates depress the reticular activating system in the brainstem, which controls consciousness. Their primary mechanism of action is through binding to the γ-aminobutyric acid type A ($GABA_A$) receptor. This site is separate from the $GABA_A$ site to which benzodiazepines bind. Barbiturates potentiate the action of GABA in increasing the duration of openings of a chloride-specific ion channel. Barbiturates also inhibit kainate and AMPA receptors.

Structure–Activity Relationships

Barbiturates are derived from barbituric acid (Figure 9–1). Substitution at carbon C_5 determines hypnotic potency and anticonvulsant activity. The phenyl group in phenobarbital is anticonvulsive, whereas the methyl group in methohexital is not. Thus methohexital remains useful for providing anesthesia for electroconvulsive therapy wherein a seizure is the objective. Replacing the oxygen at C_2 (oxybarbiturates) with a sulfur atom (thiobarbiturates) increases lipid solubility. As a result, thiopental and thiamylal have a greater potency, more rapid onset of action, and shorter duration 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).

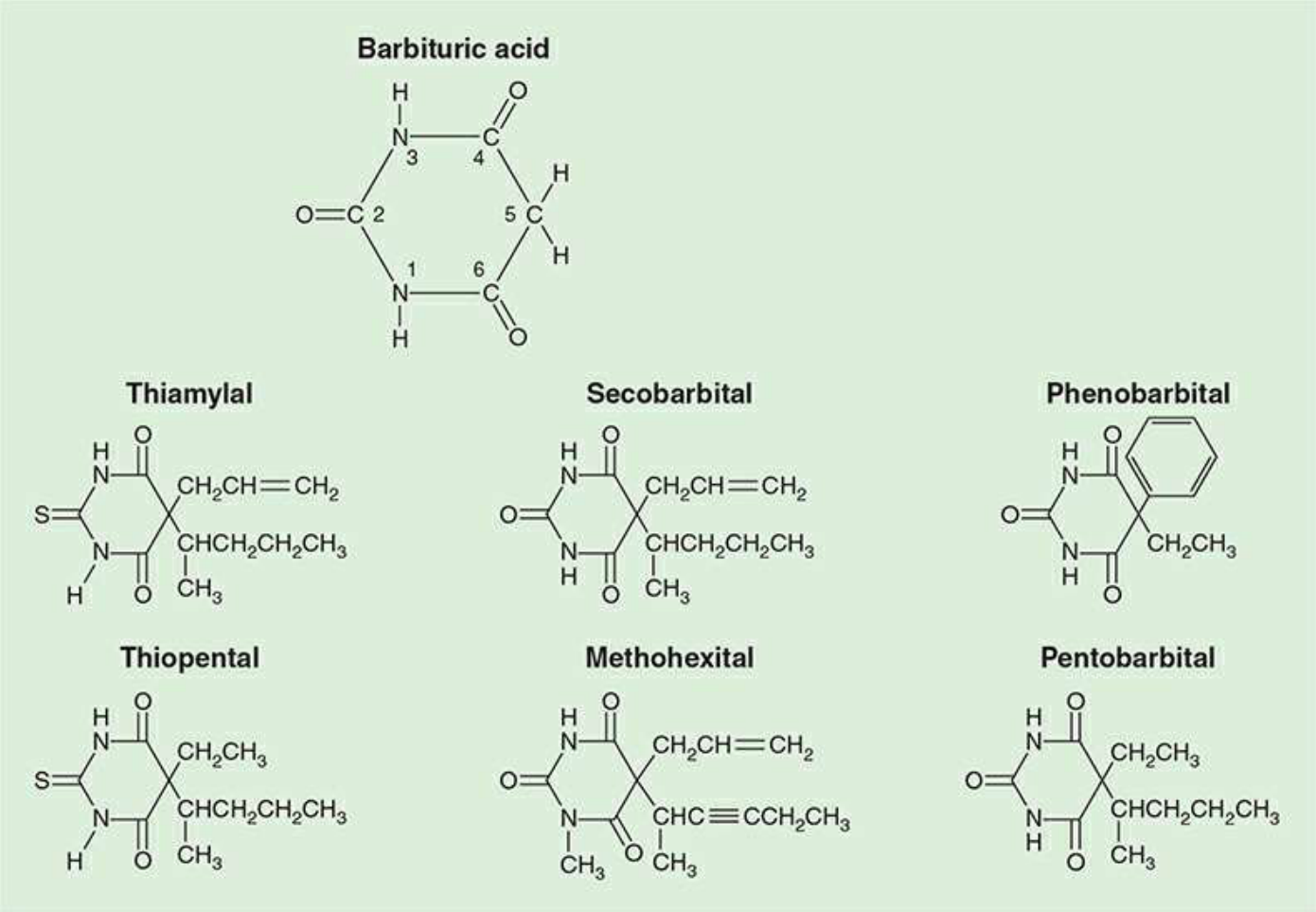

FIGURE 9–1 Barbiturates share the structure of barbituric acid and differ in the C_2, C_5, and N_1 substitutions.

Pharmacokinetics

A. Absorption

Prior to the introduction of propofol, thiopental, thiamylal, and methohexital were frequently administered intravenously for induction of general anesthesia in adults and children. Rectal methohexital has been used for induction in children.

B. Distribution

The duration of induction doses of thiopental, thiamylal, and methohexital is determined by redistribution, not by metabolism or elimination. Thiopental's great lipid solubility and high nonionized fraction (60%) 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 with greater reduction of blood pressure. Redistribution lowers plasma and brain concentration to 10% of peak levels within 20 to 30 min (Figure 9–2). This

pharmacokinetic profile correlates with clinical experience—patients typically lose consciousness within 30 s and awaken within 20 min.

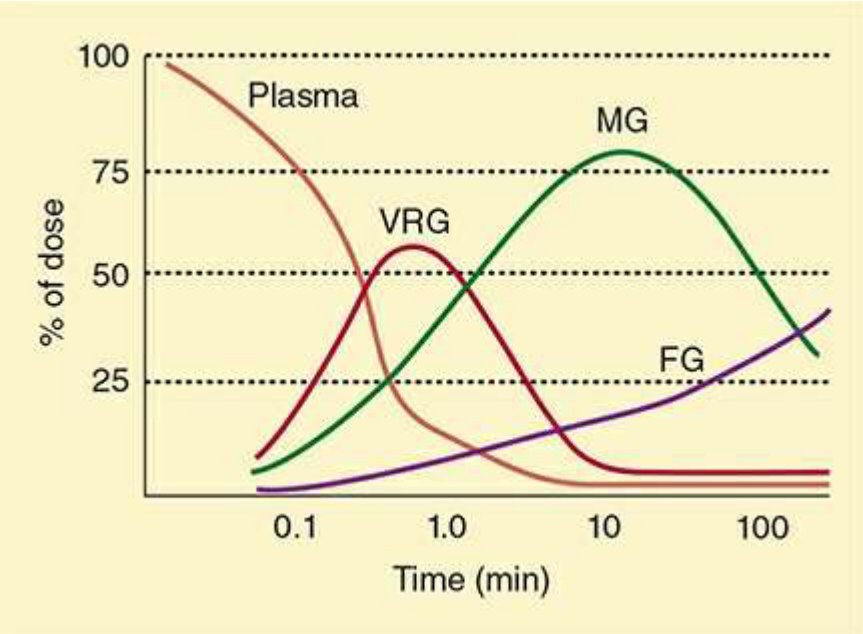

FIGURE 9–2 Distribution of thiopental from plasma to the vessel-rich group (VRG; brain, heart, liver, kidney, endocrine glands), to the muscle group (MG), and finally to the fat group (FG). Propofol follows the same pattern but on a different time scale. (Modified with permission from Price HL, Kovnat PJ, Safer JN, et al. The uptake of thiopental by body tissues and its relation to the duration of narcosis. Clin Pharmacol Ther. 1960 Jan;1(1):16-22.)

1 The minimal induction dose of thiopental will depend on body weight and age. Reduced induction doses are required for older adult patients. 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 administration of highly lipid-soluble 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, which is also seen with other lipid-soluble agents (eg, potent inhaled anesthetics, fentanyl, sufentanil; see Chapter 7).

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. Therefore, full recovery of psychomotor function is also more rapid following methohexital.

D. Excretion

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

The cardiovascular effects of barbiturates vary markedly, depending on the rate of administration, dose, volume status, baseline autonomic tone, and preexisting cardiovascular disease. A slow rate of injection with adequate preoperative hydration will attenuate or eliminate these changes in most patients. Intravenous bolus induction doses of barbiturates cause a decrease in blood pressure and an increase in heart rate. Depression of the medullary vasomotor center produces vasodilation and peripheral pooling of blood, mimicking 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.

B. Respiratory

Barbiturates depress the medullary ventilatory center, decreasing the ventilatory response to hypercapnia and hypoxia. Apnea often follows an induction dose. During awakening, tidal volume and respiratory rate are decreased. Barbiturates incompletely depress airway reflex responses to laryngoscopy and intubation (much less than propofol), and airway instrumentation may lead to bronchospasm (in asthmatic patients) or laryngospasm in lightly anesthetized patients.

C. Cerebral

Barbiturates constrict the cerebral vasculature, causing a decrease in cerebral blood flow, cerebral blood volume, and intracranial pressure. Intracranial pressure often 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 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. Small doses occasionally cause a state of excitement and disorientation. Barbiturates do not produce muscle relaxation, and some induce involuntary skeletal muscle contractions (eg, methohexital). Small doses of thiopental (50–100 mg intravenously) rapidly (but briefly) control most grand mal seizures.

TABLE 9–1 Uses and dosages of common barbiturates.

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

[1]IM, intramuscular; IV, intravenous.

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 leads to the induction of hepatic enzymes and an increased rate of metabolism. On the other hand,

the binding of barbiturates to the cytochrome P-450 enzyme system interferes with the biotransformation of other drugs (eg, tricyclic antidepressants). Barbiturates 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.

Drug Interactions

Contrast media, sulfonamides, and other drugs that occupy the same protein-binding sites may displace thiopental, increasing the amount of free drug available and potentiating the effects of a given dose. Ethanol, opioids, antihistamines, and other central nervous system depressants potentiate the sedative effects of barbiturates.

BENZODIAZEPINES

Mechanisms of Action

Benzodiazepines bind the same set of receptors in the central nervous system as barbiturates but at a different site. Benzodiazepine binding to the $GABA_A$ receptor increases the frequency of openings of the associated chloride ion channel. Benzodiazepine-receptor binding by an agonist 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 pain with intravenous or intramuscular injection.

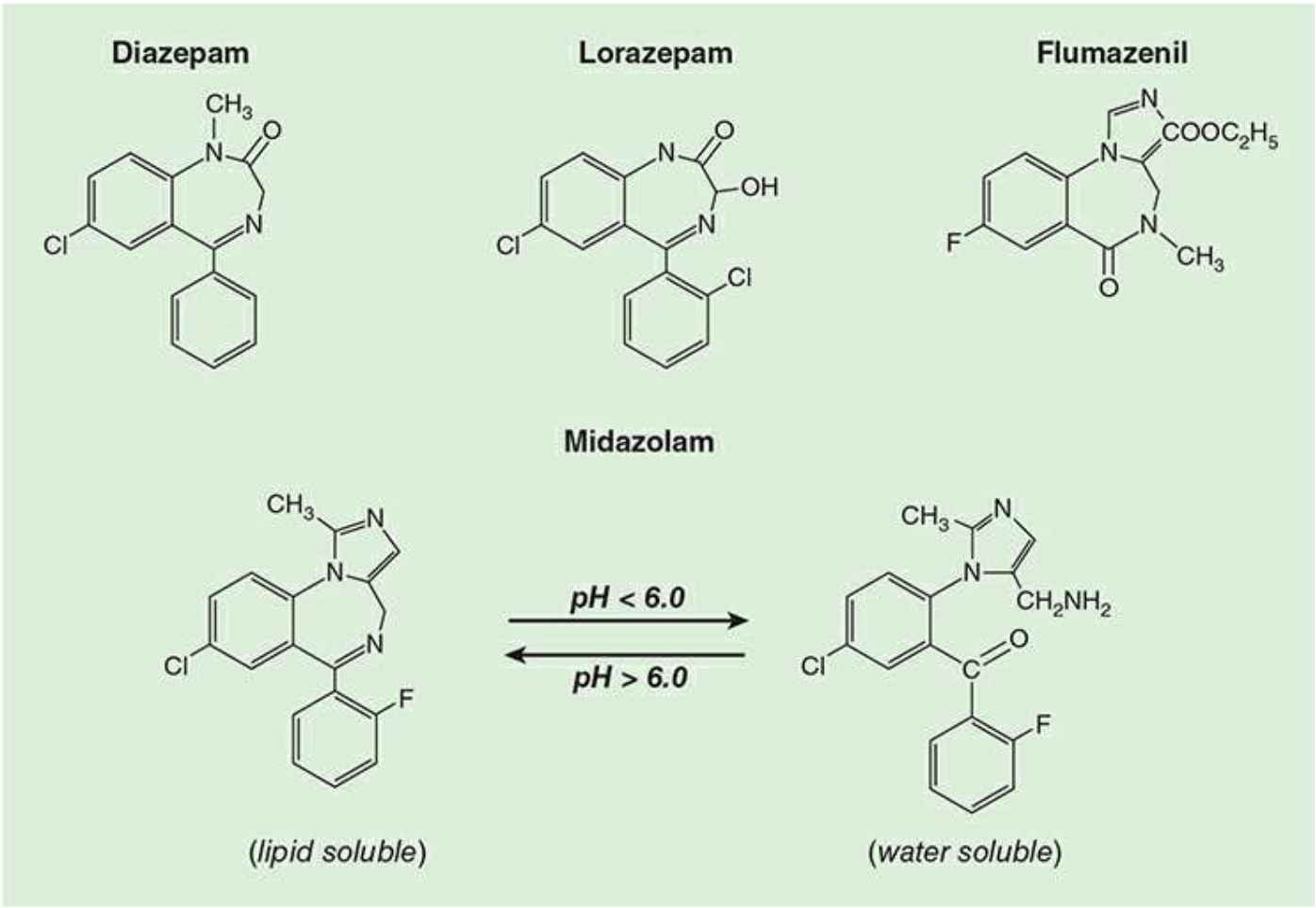

FIGURE 9–3 The structures of commonly used benzodiazepines and their antagonist, flumazenil, share a seven-member diazepine ring. (Modified with permission from White PF. Pharmacologic and clinical aspects of preoperative medication. Anesth Analg. 1986 Sep;65(9):963-974.)

Pharmacokinetics

A. Absorption

Benzodiazepines are commonly administered orally and intravenously (or, less commonly, intramuscularly) 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. Intravenous midazolam (0.05–0.1 mg/kg) given for anxiolysis before general or regional anesthesia is nearly ubiquitous. Oral midazolam (0.25–1 mg/kg), though not approved by the U.S. Food and Drug Administration for this purpose, is 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.

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

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

[1]IM, intramuscular; IV, intravenous.

Intramuscular injections of diazepam are painful and unreliably absorbed. Midazolam and lorazepam are well absorbed after intramuscular injection, with peak levels achieved in 30 and 90 min, respectively.

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 benzodiazepines and, like barbiturates, is responsible for awakening. Although we have used midazolam as an induction agent, none of the benzodiazepines can match the rapid onset and short duration of action of propofol or etomidate. 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 underscore the limited usefulness of pharmacokinetic half-lives in guiding clinical practice (see Chapter 7). 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 benzodiazepines are excreted chiefly in the urine. Enterohepatic circulation produces a secondary peak in diazepam plasma concentration 6 to 12 h following administration.

Effects on Organ Systems

A. Cardiovascular

Benzodiazepines display minimal left-ventricular 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.

B. Respiratory

Benzodiazepines depress the ventilatory response to carbon dioxide (CO_2). This depression is usually insignificant unless the drugs are administered intravenously or given with other respiratory depressants. Although apnea may be relatively uncommon after benzodiazepine induction, even small intravenous doses of these agents have resulted in respiratory arrest. The steep dose–response curve and delayed onset (compared with propofol or etomidate) necessitate titration to avoid overdosage and apnea, particularly when these agents are used for procedural sedation. Ventilation must be monitored in all patients receiving intravenous benzodiazepines (we and national advisory panels recommend end-tidal CO_2 monitoring), and resuscitation equipment and a practitioner with airway skills must be present.

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 controlling grand mal seizures. Sedative doses often produce anterograde amnesia. The mild muscle-relaxing property of these drugs is mediated at the spinal cord level. The antianxiety, amnestic, and sedative effects seen at lower doses progress to stupor and unconsciousness at anesthetic doses. Compared with propofol or etomidate, 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 the metabolism of midazolam and causes a two- to threefold

prolongation and intensification of its effects.

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 undergoing cardiac surgery who received benzodiazepines before or during induction with larger doses of opioids.

Benzodiazepines reduce the minimum alveolar concentration of volatile anesthetics by as much as 30%. Ethanol, barbiturates, and other central nervous system depressants potentiate the sedative effects of benzodiazepines.

KETAMINE

Mechanisms of Action

Ketamine has multiple effects throughout the central nervous system, and it is well recognized to inhibit N-methyl-D-aspartate (NMDA) channels. Investigators have studied ketamine actions on a long list of other ion channels and receptors; however, actions on none other than NMDA receptors appear medically important. Ketamine functionally "dissociates" sensory impulses 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 may have additional actions on endogenous analgesic pathways.

Ketamine has effects on mood, and preparations of this agent and its single enantiomer esketamine are now widely used to treat severe, treatment-resistant depression, particularly when patients have suicidal ideation. Small infusion doses of ketamine are also being used to supplement general anesthesia and to reduce the need for opioids both during and after the surgical procedure. Low-dose infusions of ketamine have been used for analgesia ("sub-anesthetic" doses) in postoperative patients and others who are refractory to conventional analgesic approaches. Ketamine has been identified by the World Health Organization as an "essential medicine."

Structure–Activity Relationships

Ketamine (Figure 9–4) is a structural analog of phencyclidine (a veterinary anesthetic and a drug of abuse). It is one-tenth as potent, yet it 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 is 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 conscious sedation during procedures such as nerve blocks and endoscopy. Even subanesthetic doses of ketamine may cause hallucinations 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. Ketamine is supplied as the racemic mixture of two optical isomers (enantiomers). 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 elsewhere throughout the world), and it has a considerably greater affinity than the racemic mixture for the NMDA receptor as well as several-fold greater potency as a general anesthetic.

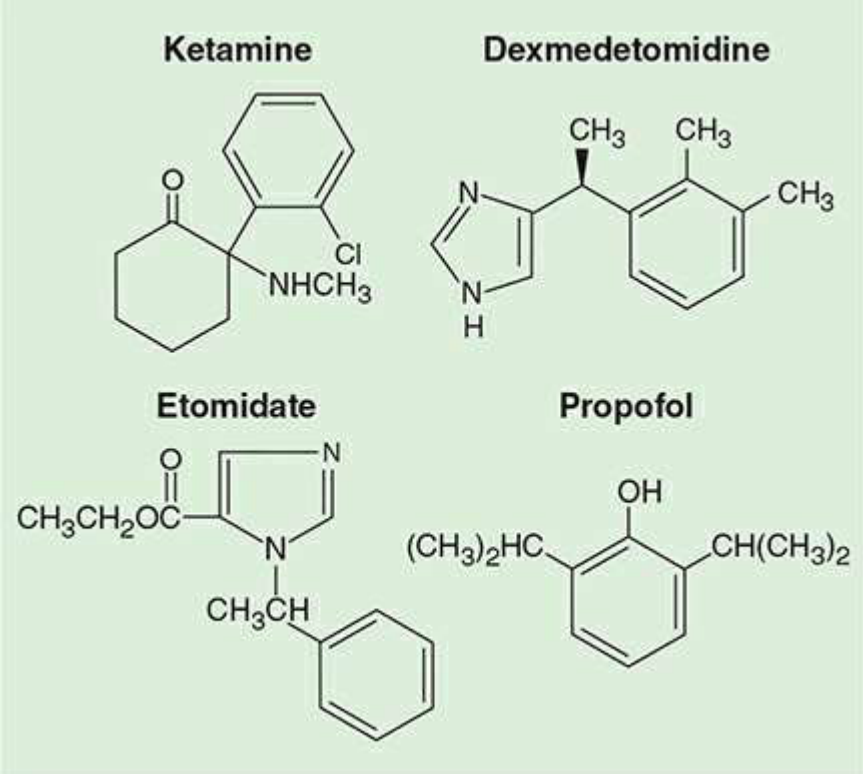

FIGURE 9–4 The structures of ketamine, etomidate, propofol, and dexmedetomidine.

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 to 15 min after intramuscular injection.

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
	Maintenance	IV	10–20 mcg/kg/min
	Analgesia or sedation	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
Dexmedetomidine	Induction	IV	1 mcg/kg over 10 min
		Nasal	1–2 mcg/kg
	Maintenance	IV	0.2–1.4 mcg/kg/h

[1]IM, intramuscular; IV, intravenous.

B. Distribution

Ketamine is highly lipid soluble and, along with a ketamine-induced increase in cerebral blood flow and cardiac output, results in rapid brain uptake and subsequent redistribution (the distribution half-life is 10–15 min). Awakening is due to redistribution from the brain to peripheral compartments.

C. Biotransformation

Ketamine is biotransformed in the liver to several metabolites, one of which (norketamine) retains anesthetic activity. Patients receiving repeated doses of ketamine (eg, for daily changing of dressings on burns) develop tolerance, and this can only be partially explained by induction of hepatic enzymes. 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

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, ketamine should be administered carefully to patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, or arterial

aneurysms. The **direct myocardial depressant** effects of large doses of ketamine may be unmasked by sympathetic blockade (eg, spinal cord transection) or exhaustion of catecholamine stores (eg, severe end-stage shock).

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	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Methohexital	↑↑	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Benzodiazepines							
Diazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Lorazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Midazolam	↑	↓↓	↓↓	0	↓↓	↓↓	↓↓
Ketamine	↑↑	↑↑	↓	↑↑↑	↑↑[2]	↑	↑↑[2]
Etomidate	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Propofol	0	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Dexmedetomidine	↓	↓	0	?	↓↓	↓↓	↓↓

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

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

B. Respiratory

Ventilatory drive is minimally affected by induction doses of ketamine, though combinations of ketamine with opioids may 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 significant 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 (in techniques that exclude 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, in patients premedicated with benzodiazepines, or in those receiving ketamine combined with propofol in a total intravenous anesthesia (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. Nondepolarizing neuromuscular blocking agents are dose-dependently, but minimally, potentiated by ketamine (see Chapter 11). Diazepam or midazolam attenuate ketamine's cardiac stimulating effects, and diazepam prolongs ketamine's elimination half-life.

α-Adrenergic and β-adrenergic antagonists (and other agents and techniques that diminish sympathetic stimulation) may 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 (mg:mg) ratio of 1:10, has achieved great popularity for procedural sedation with local and regional anesthesia or intravenous general anesthesia 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. 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% to 60% incidence of myoclonus with induction of etomidate 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 no effects on sympathetic tone or myocardial function when given by itself. A mild reduction in peripheral vascular resistance is responsible for a 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, cerebral perfusion pressure is well maintained. Although changes on EEG resemble those associated with barbiturates, etomidate (like ketamine) increases the amplitude of somatosensory evoked potentials but increases latency and reduces the amplitude of auditory evoked potentials. Postoperative nausea and vomiting are more common following etomidate than following propofol or barbiturate induction. Etomidate lacks analgesic properties.

D. Endocrine

Etomidate pharmacokinetics describes an agent that should be highly efficient for continuous infusion for TIVA or sedation. However, when infused for sedation in the intensive care unit (ICU), etomidate was reported to produce consistent adrenocortical suppression with an increased mortality rate in critically ill (particularly septic) patients. Etomidate is far more potent at inhibiting steroid production than at producing anesthesia. Induction doses of etomidate transiently inhibit CYP11B1 (in the cortisol and corticosterone pathway) and CYP11B2 (in the aldosterone synthesis pathway).

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 likely involves the facilitation of inhibitory neurotransmission mediated by $GABA_A$ receptor binding. Propofol allosterically increases the 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

6 Propofol consists of a phenol ring substituted with two isopropyl groups (see Figure 9–4). Propofol is not water soluble, but a 1% aqueous preparation (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). 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). 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 anesthetic for ambulatory surgery. A smaller induction dose is recommended in older adult 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 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. Unfortunately, this very useful device is not available in the United States.

C. Biotransformation

The clearance of propofol exceeds hepatic blood flow, implying the existence of extrahepatic metabolism. This exceptionally high clearance rate probably contributes to

rapid recovery after continuous infusions. Conjugation in the liver results in inactive metabolites that are eliminated by renal clearance. The pharmacokinetics of propofol does 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, end-stage kidney disease does not affect the 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 cardiac filling may lead to a vagally mediated reflex bradycardia (the Bezold–Jarisch reflex). Changes in heart rate and cardiac output are usually transient and insignificant in healthy patients but may be life-threatening in patients at the extremes of age, those receiving β-adrenergic blockers, or those with impaired left ventricular function. Although myocardial oxygen consumption and coronary blood flow usually decrease comparably, coronary sinus lactate production increases in some patients, indicating a 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 lesser incidence of wheezing in both asthmatic and nonasthmatic patients compared with barbiturates or etomidate.

C. Cerebral

Propofol decreases cerebral blood flow, cerebral blood volume, 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 provide a comparable degree of cerebral protection during experimental focal ischemia. Unique to propofol are its antipruritic properties. Its antiemetic effects 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. Propofol has anticonvulsant properties, has been used successfully to terminate status epilepticus, and may safely be 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, anesthesia personnel, celebrities, and other medically untrained individuals have died while using propofol inappropriately to induce sleep in nonsurgical settings.

Drug Interactions

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%. Propofol is often combined with remifentanil, dexmedetomidine, or ketamine for TIVA.

FOSPROPOFOL

Fospropofol is a water-soluble prodrug that is metabolized in vivo to propofol, phosphate, and formaldehyde. It was released in the United States (2008) 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 favor it over propofol. The place (if any) of fospropofol relative to other competing agents has not yet been established in clinical practice.

DEXMEDETOMIDINE

Dexmedetomidine is an α_2-adrenergic agonist similar to clonidine that can be used for anxiolysis, sedation, and analgesia. Strictly speaking, it is not an anesthetic in humans; however, anesthesiologists have used it in combination with other agents to produce anesthesia. It has also been used in combination with local anesthetics to prolong

regional blocks.

Most commonly, dexmedetomidine is used for procedural sedation (eg, during awake craniotomy procedures or fiberoptic intubation), ICU sedation (eg, ventilated patients recovering from cardiac surgery), or as a supplement to general anesthesia to reduce the need for intraoperative opioids or to reduce the likelihood of emergence delirium (most often in children) after an inhalation anesthetic. It has also been used to treat alcohol withdrawal and the side effects of cocaine intoxication.

Absorption

This drug is approved only for intravenous injection. Typically, intravenous dexmedetomidine sedation in awake adults is initiated with a 1-mcg/kg loading dose given over 5 to 10 min followed by a maintenance infusion of 0.2 to 1.4 mcg/kg/h. This agent can be used for premedication by nasal (1–2 mcg/kg) or oral (2.5–4 mcg/kg) administration in children, where it compares very favorably with oral midazolam.

Distribution

Dexmedetomidine has very rapid redistribution (minutes) and a relatively short elimination half-life (less than 3 h).

Biotransformation

It is metabolized in the liver by the CYP450 system and through glucuronidation. It should be used with caution in patients with severe liver disease.

Excretion

Nearly all dexmedetomidine metabolites are excreted in the urine.

Effects on Organ Systems

A. Cardiovascular

In research subjects, a loading dose of dexmedetomidine produces a small, transient increase in blood pressure accompanied by reflex bradycardia. Intraoperative infusions of dexmedetomidine typically produce dose-dependent sympatholysis with reduced mean arterial pressure and heart rate. Thus, depending on dose and rate of administration, dexmedetomidine may produce hypertension, hypotension, or bradycardia in any patient. These side effects can be minimized by avoiding rapid bolus dosing.

B. Respiratory

Dexmedetomidine produces no respiratory depression, making it nearly ideal for sedation of patients being weaned from mechanical ventilation. This agent has also been used for sedation during awake tracheal intubations.

C. Cerebral

Dexmedetomidine produces dose-dependent sedation. It is an opioid-sparing agent that can greatly reduce the requirements for general anesthetic drugs. Dexmedetomidine is the agent of choice for sedation of patients undergoing awake craniotomies.

Drug Interactions

Dexmedetomidine may cause exaggerated bradycardia in patients receiving beta-blockers, so it should be dosed carefully in such patients. It will have an additive effect on sedative–hypnotic agents.

CASE DISCUSSION

Premedication of the Surgical Patient

An extremely anxious patient presents for outpatient surgery. The patient 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 main purpose for administering premedication. For many patients, the preoperative interview with the anesthesiologist allays fears more effectively than sedative drugs. Preoperative medications may also provide relief of preoperative pain or perioperative amnesia.

There may also be specific medical indications for certain preoperative medications: prophylaxis against postoperative nausea and vomiting (5-HT_3s) and against aspiration pneumonia (eg, nonparticulate antacids) 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?

Customary levels of preoperative anxiety do not harm most patients; therefore, preoperative sedation is not a requirement for all patients. Some patients dread intramuscular injections, and others find altered states of consciousness more unpleasant than anxiety. 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 for all concerned, particularly if children have undergone 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 contribute to a 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 the choice. For instance, in a patient experiencing preoperative pain from a femoral fracture, the analgesic effects of an opioid (eg, fentanyl, morphine, hydromorphone) or ketamine 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 often administered orally. Intramuscular midazolam has a rapid onset and short duration, 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 from 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. In adults, one typically inserts an intravenous line in the preoperative holding area and titrates small doses of midazolam using slurred speech as an endpoint. At that time, the patient can be taken to the operating room. Vital signs —particularly respiratory rate—must be monitored.

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