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General Anesthesia: Intravenous and Inhalational Agents

David J. Smith and Michael B. Howie

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Anesthesia usually involves a loss of memory and awareness, along with insensitivity to painful stimuli, during a surgical procedure. Many drugs aid anesthesiologists in the management and comfort of their patients during the perioperative period. These compounds vary in their chemical and physical characteristics and in their usual routes of administration. There are inhalational agents, including volatile liquids and gases, and intravenously administered drugs.

While many of the individual compounds produce anesthesia, each one's unique pharmacokinetic and pharmacological characteristics will determine the way the practitioner uses the agent. This chapter focuses on these characteristics so that their influence on the anes-

thesiologist's choice of anesthetic technique will be understood.

Contemporary anesthetic management requires (1) rapid loss of consciousness, which eliminates awareness, memory of pain, anxiety, and stress throughout the surgical period; (2) a level of analgesia sufficient to abolish the reflex reactions to pain, such as muscular movement and cardiovascular stimulation; (3) minimal and reversible influence on vital physiological functions, such as those performed by the cardiovascular and respiratory systems; (4) relaxation of skeletal muscle to facilitate endotracheal intubation, provide the surgeon ready access to the operative field, and reduce the dose of anesthetic required to produce immobility; (5) lack of

operating room safety hazards, such as flammability and explosiveness; and (6) prompt patient recovery to psychomotor competence, facilitating the clinician's assessment of the patient and the patient's ability to become physiologically self-supporting.

While none of the anesthetic drugs discussed in this chapter possesses all of the features required for ideal anesthetic management (a summary of these features is presented in Table 25.1), the patient's needs are usually met with the use of anesthetic drugs and/or adjunctive agents, such as neuromuscular blocking drugs, opioids, and vasoactive substances. *Balanced anesthesia* is a term used to describe the multidrug approach to managing the patient's anesthetic needs. Balanced anesthesia takes advantage of each drug's beneficial effects while minimizing each agent's adverse qualities.

PHARMACOKINETIC CHARACTERISTICS INFLUENCING THE CLINICAL APPLICATION OF INTRAVENOUS AND INHALATIONAL ANESTHETICS

Intravenous anesthetics are generally employed to induce anesthesia, to provide supplemental anesthesia, or to permit anesthesia for short operative procedures. The inhalational anesthetics are most often used for longer-term maintenance of the anesthetic state. Although intravenous (IV) agents produce anesthesia rapidly, most are metabolized slowly, so recovery may be prolonged when an IV anesthetic is used as the primary drug during a long surgical procedure. In contrast, while the anesthetic partial pressure of an inhalational agent is

TABLE 25.1 General Anesthetics

Agent	Induction rate (minutes)	Anesthesia	Eliminate reflex reaction to pain	Muscle paralysis	Blood pressure ^a	Ventilation ^a	Note
Intravenous							
Thiopental (sodium pentothal)	<1	Yes	No	No	Decrease	Depressed	
Etomidate (Amidate)	<1	Yes	No	No	Minimal change	Minimal change	↓ adrenocortical response to stress
Midazolam (Versed)	<1	Yes	No	No	Minimal change	Minimal change	Water-soluble benzodiazepine
Propofol (Diprivan)	<1	Yes	No	No	Decrease	Decrease	↓ opioid requirement; antiemetic; rapid recovery via extrahepatic metabolism
Ketamine (Ketalar)	<1	Dissociative	Yes	No	Slight decrease	Minimal change	emergence delirium; IM or IV
Sufentanil (Sufenta)	<1	Incomplete amnesia?	Yes	No	Minimal change	Decrease	Anesthesia supplemented because of concern for partial awareness
Inhalational Gases							
N ₂ O	3–5	Incomplete	Yes	No	No Change	No Change	Laughing gas
Cyclopropane	3–5	Yes	Some	Some	Increase	Decrease	Flammable; explosive
Inhalational Volatile Liquids							
Sevoflurane (Ultane)	3–5	Yes	Some	Some	Decrease	Decrease	Pleasant smell; (?) nephrotoxic byproduct; combative behavior, disorientation
Desflurane (Suprane)	3–5	Yes	Some	Some	Decrease	Decrease	Bad odor; airway irritation, ↑ sympathetic outflow
Halothane (Fluothane)	10–30	Yes	Some	Minimal	Decrease	Decrease	Rare liver dysfunction
Enflurane (Ethrane)	10–30	Yes	Some	Some	Decrease	Decrease	Myoclonic
Isoflurane (Forane)	10–30	Yes	Some	Some	Decrease	Decrease	Popular inhalational agent, largely owing to cardiovascular safety
Methoxyflurane (Penthrane)	>60	Yes	Some	Minimal	Decrease	Decrease	Excessive fluoride production
Ether	>60	Yes	Yes	Yes	Increase	Increase	Flammable and explosive

^aEffects are those commonly observed in healthy patients. Poor-risk patients with significant systemic disease should be monitored for reactions of greater clinical significance.

achieved slowly, the patient recovers at a clinically acceptable rate.

Distribution of Intravenous Drugs

Intravenously administered anesthetic drugs are especially well suited to accomplish the first requirement of anesthetic management, rapid induction of unconsciousness. These compounds generally induce anesthesia within one or two circulation times after their administration because they rapidly achieve initial high concentration in the central nervous system (CNS). These drugs enter the brain because they are quite lipid soluble and consequently diffuse rapidly through all biological membranes, including the blood-brain barrier. In addition, since the brain tissue receives a large proportion of the cardiac output, a large proportion of an intravenously administered anesthetic will be distributed to the CNS. Tissues with lower blood flow per unit mass will receive and therefore remove proportionally less anesthetic during the initial phase of drug distribution. This concept is illustrated for thiopental in Fig. 25.1. All IV anesthetic drugs in use show this early pattern of distribution. The use of IV anesthetics permits the patient to pass rapidly through the initial stages of anesthesia, and sleep is induced quickly.

The initial unequal tissue–drug distribution cannot persist, however, because physicochemical forces tend to require an eventual establishment of concentration equilibria with other less well perfused organs. Therefore, as the drug continues to be removed from the blood by the less richly perfused tissues or eliminated by metabolism and excretion or both, plasma levels will fall, and the concentration of anesthetic in the brain will decline precipitously.

Tissues with an intermediate blood flow per unit of mass, such as skeletal muscle and skin, are among the first to participate in drug redistribution. In fact, it is the patient's skeletal muscle tissue groups that will contain the largest proportion of the initial dose of anesthetic when the patient awakens (Fig. 25.2). Most of the IV drugs used to induce anesthesia are slowly metabolized and excreted and depend on redistribution to terminate their pharmacological effects. The rate of initial redistribution following the administration of a single IV bolus of drug is defined by the half-life ($t_{1/2\alpha}$), and is generally about 8 minutes for most anesthetics. It can be said, therefore, that redistribution of IV anesthetics to skeletal muscle accounts for the return to consciousness after a single sleep dose of these agents. Patients generally awaken 15 to 30 minutes after a single IV injection of most of the commonly used IV anesthetics.

Poorly perfused tissues (adipose tissue, connective tissue, and bone) require hours to come into equilibrium with plasma drug concentrations (Fig. 25.1). Since the accumulation of anesthetic in body fat is relatively small soon after its IV administration, it is common clinical practice to calculate drug dosage on the basis of lean body mass rather than on total body weight. Thus, an obese patient may receive the same dose of IV anesthetic as a patient of normal body weight.

Since the distribution of blood flow is the dominant factor controlling both tissue drug levels and the accumulation of IV anesthetics, changes in cardiac output can be expected to influence the pharmacological effects of the IV anesthetics. Because blood flow to the brain is preserved, a greater proportion of the total dose of anesthetic will be delivered to the brain during times of diminished cardiac output, such as in congestive heart failure or hemorrhage. At such times, smaller

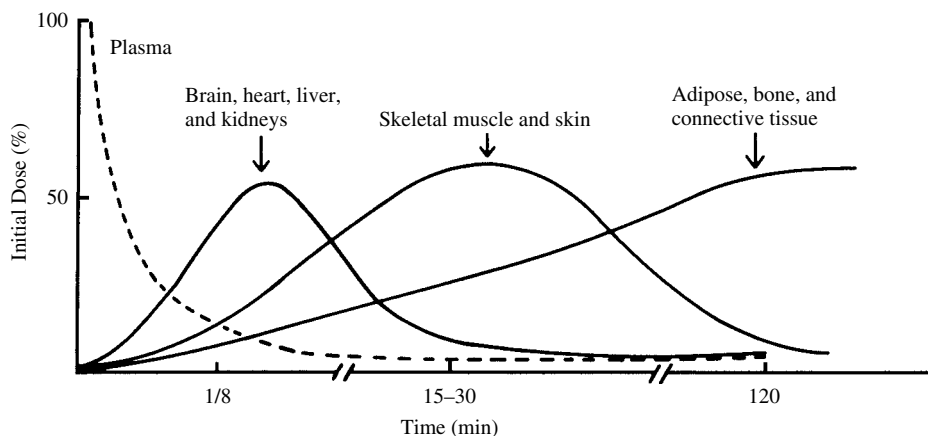


FIGURE 25.1

The distribution of thiopental in body tissues and organs following intravenous injection. Note the redistribution of the drug, with time, to tissues with lower rates of blood flow. (Reprinted 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* 1:16, 1960.)

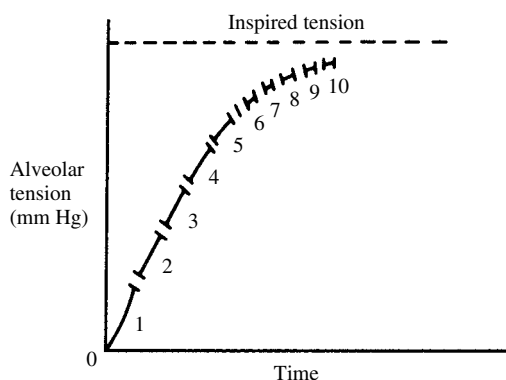


FIGURE 25.2

Alveolar tension of a hypothetical anesthetic gas of low solubility after 10 breathing cycles. Alveolar tension approaches inspired tension.

doses of anesthetic must be administered to avoid excessive CNS depression. The use of significantly lower doses of IV anesthetic drug also should be a consideration in elderly patients, since they have low cardiac output, low lean body mass, and frequently a reduced capacity for drug clearance.

The effect of increased cardiac output on the administered dose of anesthetic is opposite that discussed for reduced cardiac output. Intensely anxious patients and those who have such diseases as thyrotoxicosis usually require larger doses of anesthetic to induce anesthesia.

Metabolism and Excretion of Intravenous Drugs

Clearance of IV anesthetics from the body eventually requires metabolism and excretion. Since *drugs with long elimination half-lives ($t_{1/2\beta}$) will have slow rates of clearance*, their use by repeated IV bolus or continuous infusion to maintain anesthesia has been restricted. Long-term application with limited concern for the pharmacokinetics of the agents may lead to delayed awakening, as large quantities of these drugs may accumulate in reservoir tissues, such as skeletal muscle and fat. Thus, after lengthy anesthetic administration, drug plasma levels will remain high as the compound diffuses from these tissue reservoirs. On the other hand, if the duration of an infusion remains short, awakening may be nearly the same with drugs exhibiting short and long elimination half-lives. With a shorter infusion, the quantities of drug accumulated in reservoir tissues are not sufficient to maintain high plasma and brain levels. Thus, length of infusion is a context in which the duration of drug action is considered. The term *context sensitive half-time* has been coined to express the effect of duration of infusion (the context) on plasma levels of infused drugs.

Administration of Intravenous Anesthetics by Controlled Infusion

The recent advent of computer-assisted IV drug administration has made more practical the maintenance of anesthesia with anesthetics with relatively short half-lives (e.g., propofol and short-acting phenylpiperidine opioids). The technique called *total intravenous anesthesia (TIVA)* is done with short-acting drugs so that rapid recovery occurs even after long infusions. The loading and maintenance doses of each agent can be programmed by taking their individual pharmacokinetic profiles into consideration. Thus, dosage is automatically adjusted for factors that may alter drug distribution, parameters controlling drug clearance, and the duration of the procedure, to maintain a plasma level that is just adequate for the appropriate depth of anesthesia. Many practitioners, however, still prefer to titrate the infusion of intravenous drugs to effect without the use of computer programming.

The shorter-acting drugs seem to have increasing applications in outpatient surgery, which now accounts for nearly 60% of all elective procedures, and for minor inpatient procedures (e.g., wound repair, bronchoscopy, angiography). Patients generally receive lower doses of drugs so that operative procedures are tolerable, avoiding the substantial depression of cardiorespiratory systems that may occur with the higher doses required for hypnosis. Sedative doses of benzodiazepines and propofol are among the most common; they are frequently administered in combination with short-acting opioids. The term for such a technique is *conscious sedation*. Other techniques may also be employed. For example, when an opioid is combined with a neuroleptic drug, such as the butyrophenone droperidol (*Inapsine*), the technique is called *neuroleptanalgesia*. An inhalational drug, such as nitrous oxide (N_2O), may be added during intervals of the operative procedure when complete anesthesia is desired (i.e., neuroleptanesthesia).

INTRAVENOUS ANESTHETIC AGENTS

Important pharmacological characteristics for anesthetic management using IV anesthetics are shown in Table 25.1. The principal use of these drugs is to induce anesthesia. In typical anesthetic management, the last event that the patient remembers is the insertion of the needle. Patients are often unaware that other anesthetics, most frequently in the form of inhalational drugs, are necessary to maintain the anesthesia.

Ultra-Short-Acting Barbiturates

Among the barbiturates (see Chapter 30), three compounds, thiopental sodium (*Pentothal Sodium*), thiamylal sodium (*Surital*), and methohexital sodium (*Brevital*)

Sodium), are useful as induction agents, as supplemental drugs only during short periods when surgery requires increased depth of anesthesia, or as maintenance hypnotics for short surgical procedures. These drugs are termed *ultra-short-acting* agents, since their rapid entry into the CNS is followed by relatively rapid redistribution of the drug to indifferent tissues, such as skeletal muscle. Because of their slow rate of metabolism, these agents, when used in large repeated doses or by continuous infusion, cause persistent hypnosis or subtle mental cloudiness.

Pharmacological Actions

All three IV barbiturates rapidly produce unconsciousness. Since unconsciousness is attended by amnesia without either analgesia or skeletal muscle relaxation, anesthetized patients may react to painful stimuli but are unaware and do not remember the procedure. For example, patients undergoing short surgical procedures with thiopental alone may respond to surgical maneuvers with facial grimaces or arm and leg movements and with potentially dangerous changes in blood pressure and heart rhythm. Consequently, induction of anesthesia may be nearly the only indication for thiopental. However, if thiopental is to be used to maintain anesthesia for short operative procedures, analgesia should be provided with other drugs.

Thiopental remains the most popular IV induction agent. Its rapid and pleasant induction of anesthesia and its relatively low cost are among the reasons for its high acceptance rate by both the patient and the practitioner. Also, it does not induce obstructive secretions in the airway, produces little or no emesis, and does not sensitize the myocardium to endogenous catecholamines that may be released in response to the stress of surgery. It can, however, cause cardiovascular depression.

Although the pharmacological actions of the IV barbiturates are similar, methohexital in particular may provide some advantages in selected situations. Its duration of action is only half as long, and it exerts fewer cumulative effects than does thiopental. The occasional requirement of intraoperative communication between the patient and surgeon is easily satisfied with methohexital because of its short duration of action. For example, it can be used for basal sedation in the few moments that a very painful stimulus is applied, and then, as consciousness is quickly regained, the surgeon can assess the results by talking to the patient.

Adverse Effects

Cardiovascular depression may occur after the administration of barbiturates by IV bolus. The hemodynamic changes are transient in the healthy patient with good cardiovascular reserve, but they may be prolonged

and/or not well tolerated in elderly patients or those with poorly compensated myocardial function. For example, thiopental decreases myocardial contractility and dilates capacitance vessels, thereby reducing venous return to the heart. The healthy normovolemic patient may compensate for these changes by an increase in heart rate to maintain stroke volume and blood pressure. The patient with myocardial disease or hypovolemia may not be capable of appropriate compensation. Serious ischemic impairment of the myocardium may occur in patients with coronary artery disease.

Respiratory depression also may occur after the administration of barbiturates by IV bolus. Respiration may be further compromised by barbiturate-induced laryngospasm, as it is with most anesthetics.

There is some tendency of the ultra-short-acting barbiturates to precipitate at biological pH once they are injected, especially if the injection solution is not given slowly enough to allow the drug to be diluted by the venous blood. If inadvertent intraarterial injection occurs and drug precipitates are formed, arterial thrombosis, vasospasm, local ischemia, and possibly tissue sloughing may occur. Methohexital precipitation is less common, since it is a more potent barbiturate and can be provided in a more dilute solution. Barbiturate solutions must not be coadministered with acidic solutions, such as those containing meperidine, morphine, or ephedrine.

Most of the adverse reactions associated with the use of the intravenous barbiturates are predictable and therefore can be controlled or avoided. Some reactions, such as hypersensitivity, are entirely unpredictable. Particularly patients with asthma, urticaria, or angioedema may acquire allergic hypersensitivity to the barbiturates. Acute intermittent porphyria is an absolute contraindication to the use of barbiturates.

Benzodiazepines

Midazolam (*Versed*), diazepam (*Valium*), and lorazepam (*Ativan*) are benzodiazepine derivatives that are useful in anesthesia. Midazolam is the most popular of these agents for the induction of anesthesia. Its popularity is related to its aqueous solubility and to its short duration of action, which permits a prompt return of psychomotor competence. Unlike midazolam, lorazepam and diazepam are not water soluble and must be formulated in propylene glycol; the latter is irritating to the vasculature on parenteral administration.

Benzodiazepines are useful as orally administered premedications. They are also used intravenously in doses that produce conscious sedation rather than hypnosis. Sedated patients tolerate unpleasant procedures (e.g., wound repair, bronchoscopy, angiography) while maintaining cardiorespiratory function and the ability to respond to tactile stimulation or verbal commands.

Midazolam has a shorter half-life ($t_{1/2\beta} = 1.3\text{--}2.2$ hours) than either diazepam ($t_{1/2\beta} = 30$ hours) or lorazepam and is not converted in the liver to active metabolites, as is diazepam. Thus, use of midazolam results in a more rapid return to psychomotor competence. Doses may need to be lowered by at least 30% in older patients and in those premedicated with opioids or other sedative drugs.

Pharmacological Actions

The benzodiazepines, when given by slow IV infusion to induce anesthesia, have minimal influences on the cardiovascular and respiratory systems. Thus, they may be logical substitutes for barbiturates in poor-risk patients who cannot tolerate cardiovascular depression. In other respects, they appear pharmacologically similar to the barbiturates. IV administration causes unconsciousness without analgesia; skeletal muscle relaxation is inadequate for intubation or short surgical procedures. Consequently, when these characteristics of anesthetic management are desired, benzodiazepines must be coadministered with appropriate analgesic drugs and neuromuscular blocking agents.

The popularity of the benzodiazepines as an anesthetic supplement in cardiac surgery is related to their amnesic potential. They can ensure unawareness during the initial period, when the anesthetics are being diluted in the fluid of the bypass circuit. Lorazepam is often chosen for this purpose because it is longer acting and more potent than either midazolam or diazepam. Benzodiazepine administration may cause amnesia even when used in doses that do not produce unconsciousness. Antegrade amnesia may occur with the doses that are used to relieve preoperative anxiety.

Benzodiazepine Antagonist

Flumazenil (*Romazicon*) is a benzodiazepine antagonist that specifically reverses the respiratory depression and hypnosis produced by the benzodiazepine receptor agonists. Its block of the amnesic effect of the agonists is less reliable. Flumazenil is particularly useful when an overdose of benzodiazepines has occurred. It is also employed when a benzodiazepine has been used to produce conscious sedation and rapid recovery of psychomotor competency is desirable. To avoid re sedation, flumazenil may require administration by intravenous infusion.

Etomidate

The pharmacological properties of etomidate (*Amidate*) are similar to those of the barbiturates, although its use may provide a greater margin of safety because of its limited effects on the cardiovascular and respiratory systems. Since it has a relatively short elimination half-life ($t_{1/2\beta} = 2.9$ hours), in addition to its use as an induc-

tion agent, etomidate has been used as a supplement to maintain anesthesia in some critically ill patients. Etomidate is rapidly hydrolyzed in the liver.

Pharmacological Actions

A primary advantage of etomidate is its ability to preserve cardiovascular and respiratory stability; both cardiac output and diastolic pressure are well maintained. Use of etomidate may offer some advantage to the patient with compromised myocardial oxygen or blood supply or both, since it produces mild coronary vasodilation. Thus, coronary vascular resistance decreases with no change in perfusion pressure. Preservation of diastolic perfusion pressure may be particularly important when myocardial blood supply cannot be increased by autoregulation.

Adverse Effects

Etomidate may cause pain on injection and may produce myoclonic muscle movements in approximately 40% of patients during its use as an induction anesthetic. In addition, etomidate can suppress the adrenocortical response to stress, an effect that may last up to 10 hours.

Propofol

Propofol (*Diprivan*) is rapidly acting, has a short recovery time, and possesses antiemetic properties. A rapid onset of anesthesia (50 seconds) is achieved, and if no other drug is administered, recovery will take place in 4 to 8 minutes. The recovery is attributed to redistribution of the drug and rapid metabolism to glucuronide and sulfate conjugates by the liver and extrahepatic tissues, such as intestine and kidney.

Rapid recovery and its antiemetic properties make propofol anesthesia very popular as an induction agent for outpatient anesthesia. Propofol can also be used to supplement inhalational anesthesia in longer procedures. Both continuous infusion of propofol for conscious sedation and with opioids for the maintenance of anesthesia for cardiac surgery are acceptable techniques.

Pharmacological Actions

Propofol is primarily a hypnotic drug with substantial cardiorespiratory depressant actions and with no ability to produce neuromuscular blockade. While propofol lacks analgesic properties, its use permits lower doses of opioids. Likewise, less propofol is required for adequate hypnosis when it is administered with opioids. Thus, it is said that propofol and opioids interact synergistically.

Adverse Effects

The dose of propofol should be reduced in older patients; however, it does have a relatively linear dose-response characteristic, and patients generally can be

safely titrated. The pain on injection, especially when small veins are used, can be considerably reduced if lidocaine 20 mg is administered first.

Anesthesia induction with propofol causes a significant reduction in blood pressure that is proportional to the severity of cardiovascular disease or the volume status of the patient, or both. However, even in healthy patients a significant reduction in systolic and mean arterial blood pressure occurs. The reduction in pressure appears to be associated with vasodilation and myocardial depression. Although propofol decreases systemic vascular resistance, reflex tachycardia is not observed. This is in contrast to the actions of thiopental. The heart rate stabilization produced by propofol relative to other agents is likely the result of either resetting or inhibiting the baroreflex, thus reducing the tachycardic response to hypotension.

Since propofol does not depress the hemodynamic response to laryngoscopy and intubation, its use may permit wide swings in blood pressure at the time of induction of anesthesia. Propofol should be used with utmost caution in patients with cardiac disease.

Ketamine

Ketamine is a cyclohexanone derivative whose pharmacological actions are quite different from those of the other IV anesthetics. The state of unconsciousness it produces is trancelike (i.e., eyes may remain open until deep anesthesia is obtained) and cataleptic; it has frequently been characterized as dissociative (i.e., the patient may appear awake and reactive but does not respond to sensory stimuli). The term *dissociative anesthesia* is used to describe these qualities of profound analgesia, amnesia, and superficial level of sleep.

Pharmacological Actions

Slow IV administration of ketamine does not cause gradual loss of airway reflexes, apnea, or general muscular relaxation. The onset of the ketamine-induced “anesthetic state” is accompanied by a gradual, mild increase in muscle tone (which greatly resembles catatonia), continued maintenance of pharyngeal and laryngeal reflexes, and opening of the eyes (usually accompanied by nystagmus). Although reflexes may be maintained, the airway still must be protected, since ketamine sensitizes laryngeal and pharyngeal muscles to mucous or foreign substances, and laryngospasm may occur.

Ketamine also can be contrasted to other intravenous drugs in its ability to cause cardiovascular stimulation rather than depression. The observed increases in heart rate and blood pressure appear to be mediated through stimulation of the sympathetic nervous system. In a healthy, normovolemic, unpremedicated patient, the initial induction dose of ketamine maintains or stimulates cardiovascular function. In contrast, patients with

poor cardiac reserve, compromised autonomic control, or hypovolemia may undergo a precipitous fall in blood pressure after induction of anesthesia with ketamine. If selection of the patient and preoperative preparation are carefully done, however, ketamine may be an excellent drug for the induction of anesthesia in individuals who cannot tolerate compromise of their cardiovascular system.

The analgesia induced by ketamine also is a property that separates it from other IV anesthetic drugs. Analgesia is obtained without a deep level of anesthesia. When subdissociative doses of ketamine are given either IV or intramuscularly (IM), they provide adequate analgesia for postoperative pain relief as well as analgesia for brief operations on the skin, such as debridement of third-degree burns. Because it can be regarded as a nearly complete anesthetic (hypnosis and analgesia), does not require anesthesia equipment, and is relatively protective of hemodynamics, ketamine also can be very useful outside of normal operating room conditions, such as may be found during painful radiographic procedures.

A most important advantage of ketamine over other anesthetic agents is its potential for administration by the IM route. This is particularly useful in anesthetizing children, since anesthesia can be induced relatively quickly in a child who resists an inhalation induction or the insertion of an IV line. Ketamine has a limited but useful role as an IM induction agent and in pediatrics.

Adverse Effects

The most serious disadvantage to the use of ketamine is its propensity to evoke excitatory and hallucinatory phenomena as the patient emerges from anesthesia. Patients in the recovery period may be agitated, scream and cry, hallucinate, or experience vivid dreams. These episodes may be controlled to some extent by maintaining a quiet reassuring atmosphere in which the patient can awaken or if necessary by administering tranquilizing doses of diazepam.

Other reported side effects include vomiting, salivation, lacrimation, shivering, skin rash, and an interaction with thyroid preparations that may lead to hypertension and tachycardia. Ketamine also may raise intracranial pressure and elevate pulmonary vascular resistance, especially in children with trauma or congenital heart disease. Increases in intraocular pressure also may occur, and vigilance is required if ketamine is used in ocular surgery.

Intravenous Anesthetic Techniques Managed with Opioids

Opioid analgesics have always been important for the control of pain in the preoperative and postoperative periods. They are also used to supplement anesthesia

when other anesthetic drugs do not adequately control pain reactions. Recently, the more potent and rapidly acting phenylpiperidine opioids have been used as induction agents or as the primary drug for the maintenance of anesthesia (opioid anesthesia), particularly when hemodynamic stability is essential. The high doses required to produce unconsciousness do not depress the myocardium, nor do they cause a significant reduction in blood pressure. Doses must be at least 10 times those used for the control of pain in ambulatory patients; thus, the anesthetic approach is often referred to as high-dose opioid. The opioids most commonly used are the highly potent, short-acting phenylpiperidine compounds (see Chapter 26), such as fentanyl (*Sublimaze*), sufentanil citrate (*Sufenta*), alfentanil (*Alfenta*) and remifentanil (*Ultiva*). Compared to fentanyl and sufentanil, alfentanil has a shorter duration of action because of pharmacokinetic characteristics that favor its sequestration in plasma (i.e., high protein binding and relatively low lipid solubility).

Remifentanil, recently approved for use in the United States and Europe, is the first truly ultra-short-acting opioid. Remifentanil's unique ester linkage allows it to be rapidly degraded to an inactive carboxylic acid metabolite by nonspecific esterases found in tissue and red blood cells. Since it is not a good substrate for plasma pseudocholinesterase, deficiency of the enzyme does not influence its duration of action. Also, hepatic and renal insufficiencies do not influence remifentanil's pharmacokinetics, so it is useful when liver or kidney failure is a factor. Because of its rapid clearance following infusion, remifentanil has gained popularity as an agent for maintenance of anesthesia when an IV technique is practical.

Although opioid anesthesia is particularly useful in patients with compromised myocardial function, the opioids depress respiration by inhibiting the responsiveness of the medullary respiratory center to PCO_2 and alter the rhythm of breathing. Consequently, it is necessary to assist ventilation intraoperatively. Since respiratory depression may extend into the postoperative period as a result of drug accumulation in the tissues, the use of opioids whose clearances are slow, remain most appropriate for patients who are expected to require postoperative ventilatory care.

Less potent opioids have fallen into disfavor because of the prominence of the untoward effects they produce when given in high doses. Meperidine hydrochloride (*Demerol*) causes tachycardia, while morphine produces hypotension and bronchoconstriction as a consequence of its histamine-releasing action.

Opioid-induced muscle rigidity is a frequent complication of this form of anesthesia. It is most common with phenylpiperidine drugs and occurs even after low doses of fentanyl, such as those used in certain diagnostic or minor surgical procedures where a pain-free

but communicative patient is required (i.e., neuroleptanalgesia; conscious sedation). Rigidity affects the chest wall and abdomen and thus significantly interferes with breathing. The problem may result from an opioid-induced stimulation of spinal reflexes or interference with basal ganglia integration; the rigidity can be controlled through the use of neuromuscular blocking agents (e.g., pancuronium) and ventilatory support.

One of the most serious drawbacks of opioid anesthesia is the possibility of inadequate anesthetic depth. Signs of inadequate anesthesia include sweating, pupillary dilation, wrinkling of the forehead, and opening of the eyes. Most important, however, awareness or incomplete amnesia may occur. Consequently, additional doses of the opioids are appropriate when signs of light anesthesia manifest. Furthermore, many clinicians supplement the high-dose opioid technique with inhalational anesthetics or hypnotics, such as benzodiazepines (midazolam for shorter cases; the longer-acting drug lorazepam for cases longer than 4 hours) or more recently, propofol. Unfortunately, the use of many of these supplemental drugs may result in some loss of cardiovascular stability.

α_2 -Adrenoceptor Agonists

α_2 -Adrenoceptor agonists have received attention for their ability to produce sedation and analgesia. Their sedative properties may be related to action on α_2 -receptors in the locus ceruleus, and analgesia likely occurs via α_2 -receptors in the spinal cord and locus ceruleus. Agents used when sedation is desirable include oral clonidine (*Catapres*) and IV dexmedetomidine (*Precedex*), which has recently been approved in the United States for sedation in intensive care units. A solution of clonidine (*Duraclon*) is also available to provide or as a supplement for epidural analgesia. Hypnosis sufficient for surgical anesthesia is not adequate when the α_2 -adrenoceptor agonists are used alone, and cardiovascular side effects, including bradycardia and hypotension, limit the doses that can be used. As adjunctive drugs they significantly reduce the dose requirement for opioids and anesthetics during surgery.

INHALATIONAL ANESTHETICS

The inhalational anesthetics can be divided into two classes based on their physical properties. N_2O and cyclopropane are gases at room temperature and are supplied in gas tanks that are regulated by the anesthesia machine. The others are liquids that are volatile following the application of low heat, which is supplied by a vaporizer attached to the anesthesia machine. The halogenated hydrocarbons are among the most potent volatile anesthetics.

Pharmacokinetic Characteristics

The use of inhalational anesthetics is generally reserved for maintenance of anesthesia. The development of an anesthetic concentration in the brain occurs more slowly with inhalational anesthetics than with IV drugs. Once an anesthetic level has been achieved, however, it is easily adjusted by controlling the rate or concentration of gas delivery from the anesthesia machine. The rate of recovery from a lengthy procedure in which inhalational agents are used is reasonably rapid, since inhalational anesthetics are eliminated by the lungs and do not depend on a slow rate of metabolism for their tissue clearance. Thus, inhalational drugs meet the requirement for a relatively prompt return of the patient's psychomotor competence.

Pharmacokinetic factors that influence the distribution of gases control the establishment of anesthetic concentrations in tissue. Thus, factors influencing gas distribution in tissues are important to the anesthesiologist, who must control anesthetic delivery and adjust for physiological influences and/or pathological conditions that can alter the accumulation of the gas. Unlike most drugs whose equilibration with tissues involves concentration gradients, partial pressure gradients control the equilibration of gases between various tissue compartments.

Development of the Partial Pressure of a Gas in Solution

Henry's law explains the behavior of gases in solutions and can be extended to body tissues. In many ways, inhalation anesthetic agents appear to be inert gases that interact with tissues and liquids physically rather than chemically. Therefore, laws governing the physical association of gases and liquids are of paramount importance to an understanding of the pharmacokinetics of these drugs. Henry's law describes the regulation of a gas concentration in a liquid when the association of these two phases is through physical interaction alone. The law states that at equilibrium, the concentration of gas physically dissolved in a liquid is directly proportional to the partial pressure (or tension) of the agent and its affinity for the molecules of the liquids (or its solubility in the liquid).

For a clear understanding of Henry's law, it is important to consider each of its component parts.

Partial Pressure of Gas Molecules in a Liquid

Inherent in Henry's law is the concept that when a liquid is exposed to a gas, a partial pressure equilibrium will be achieved between the gas and liquid phases. Thus, molecules of the gas that are physically dissolved in the liquid will exert tension that is equal to the partial pressure of the gas above the liquid. It is not neces-

sary that a defined gas space, such as a bubble, exist before pressure can be generated. Individual molecules of gas become surrounded and separated by liquid or tissue molecules. Furthermore, since they are inert and do not combine chemically with the solvent, the gas molecules remain independent and therefore are free to undergo random molecular motion and exert pressure equal to that in the gas phase.

Practically speaking, this concept explains the basis for the establishment of partial pressure equilibrium of anesthetic gas between the lung alveoli and the arterial blood. Gas molecules will move across the alveolar membrane until those in the blood, through random molecular motion, exert pressure equal to their counterparts in the lung. Similar gas tension equilibria also will be established between the blood and other tissues. For example, gas molecules in the blood will diffuse down a tension gradient into the brain until equal random molecular motion (equal pressure) occurs in both tissues.

Affinity of Gas Molecules for Solvent Molecules

A primary force opposing random molecular motion is the affinity of gas molecules for the tissue in question (a second factor in Henry's law that expresses the degree of solubility of that agent in the tissue). If a particular gas has a strong affinity for the molecules of a solvent, its random molecular motion will be impeded by a great number of collisions with the solvent molecules. Therefore, it will require a greater volume of an agent of high affinity (or greater solubility) to enter a tissue to generate the same partial pressure as does an agent of low affinity (or lower solubility).

Concentration of Anesthetic Gas in a Tissue

The anesthesiologist can control brain concentration of gas only by modifying the partial pressure of the agent that is delivered to the alveoli. The gas then diffuses across the alveolus to the blood and ultimately into the CNS. The final concentration of gas in the tissue is a function of the partial pressure and the affinity for the tissue (i.e., Henry's law).

A Concept of Anesthetic Dose Based on Partial Pressure—Minimum Alveolar Concentration

Since the anesthesiologist has control over the partial pressure of anesthetic delivered to the lung, it can be manipulated to control the anesthetic gas concentration in the brain, hence the level of unconsciousness. For this reason, anesthetic dose is usually expressed in terms of the alveolar tension required at equilibrium to produce a defined depth of anesthesia. The dose is determined experimentally as the partial pressure needed

to eliminate movement in 50% of patients challenged with a standardized skin incision. The tension required is defined as the minimum alveolar concentration (MAC) and is usually expressed as the percentage of inhaled gases that is represented by anesthetic gas at 1 atm.

Various anesthetic agents require widely different partial pressures to produce the same depth of anesthesia (Table 25.2). Methoxyflurane, for example, with a MAC of 0.16%, is the most potent agent listed in the table. Only 0.16% of the molecules of inspired gas need be methoxyflurane. N₂O is the least potent agent, with a MAC that exceeds 100%. Thus, a level of unconsciousness needed to eliminate movement is seldom achieved with N₂O.

Clinical Application and Interpretation of MAC

MAC is a valuable index for clinical anesthesia, but it is seldom employed without taking other factors into consideration. For example, inhibiting movement in only 50% of patients is not acceptable. Consequently, if an inhalational agent were being used alone—that is, without the administration of other anesthetics or analgesic drugs—the anesthesiologist would employ a multiple of its MAC value to ensure immobility. MAC is frequently multiplied by a factor of 1.3 to achieve nearly 100% clinical efficacy. On the other hand, useful clinical results may be achieved with doses of anesthetics below MAC levels. For example, mild analgesia and amnesia often occur with doses of inhalational agents that are near 0.5 MAC. In this state, it may even be possible to communicate with patients intraoperatively, while their recall is limited.

Anesthetics are infrequently used without the administration of other drugs. Many of these drug combinations can interact to alter MAC requirements. For example, inhalational anesthetics used in combination

appear to have an additive effect on the level of unconsciousness. Therefore, when a combination of inhalational agents is used (e.g., N₂O with halothane), MAC values for the individual agents can be reduced appropriately. In this regard, an acceptable anesthetic maintenance tension for N₂O and halothane in the inspired air may be 40% and 0.5%, respectively.

The MAC requirement also is reduced by the coadministration of other CNS depressants, such as barbiturates or opioid analgesics. CNS stimulants, such as amphetamine, may elevate the partial pressure needed for anesthesia.

Factors Affecting the Rate of Development of Anesthetic Concentration in the Lung

Gases diffuse from areas of high partial pressure to areas of low partial pressure; thus, the tension of anesthetic in the alveoli provides the driving force to establish brain tension. In fact, the tension of anesthetic in all body tissue will tend to rise toward the lung tension as equilibrium is approached. Consequently, factors that control or modify the rate of accumulation of anesthetic in the lung (e.g., rate of gas delivery, uptake of gas from the lung into the pulmonary circulation) will simultaneously influence the rate at which tension equilibria in other body compartments is established.

Graphs of the alveolar tension plotted against time are used in this chapter to illustrate the changes in lung partial pressure as anesthetic is inhaled. Only a fraction of total lung gases are exchanged during one breathing cycle. Therefore, the volume of gases already in the lung dilutes the first breath of anesthetic (breathing cycle 1 in Fig. 25.3). In subsequent breathing cycles, the alveolar tension will continue to rise toward the inspired level along an exponentially declining curve. The net change of anesthetic tension becomes smaller with each breathing cycle, and the curve of alveolar tension will approach the inspired level more slowly.

The alveolar tension–time curve always declines in an exponential manner, but the position of the curve can be greatly affected by the rate of delivery of anesthetic gases and the rate of their uptake into the pulmonary circulation. For this reason, it is important to consider factors that modify or regulate delivery and uptake.

Effect of the Alveolar–Arterial Tension Gradient on Alveolar Tension of Anesthetic Gas

Tissues, including the brain, that have a high blood flow per unit mass (Fig. 25.1) equilibrate with the alveolar tension of anesthetic gases first. Tissues with lower blood flow require a longer time and continue to accumulate anesthetic gas during the maintenance phase of

TABLE 25.2 Minimum Alveolar Concentration in Oxygen^a

Nitrous oxide	>100.00 ^b
Desflurane	6.00
Sevoflurane	2.05
Enflurane	1.68
Isoflurane	1.15
Halothane	0.75
Methoxyflurane	0.16

^aExpressed as the percent of lung gases that are anesthetic gas at 1 atm.

^bMAC value greater than 100 indicates that hyperbaric conditions are required to produce anesthesia.

Adapted with permission from Eger EI II (ed.). *Anesthetic Uptake and Action*. Baltimore: Williams & Wilkins, 1974: 5; Eger EI. Isoflurane: A review. *Anesthesiology* 1981;55:559.

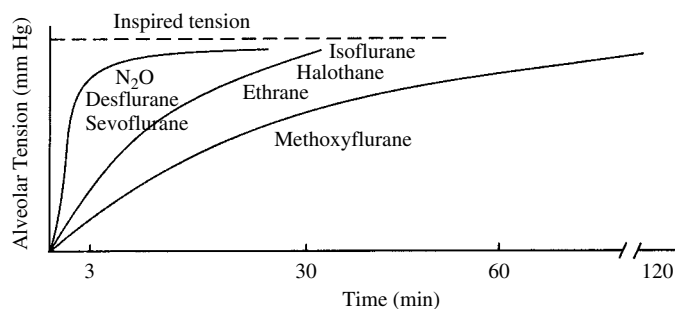


FIGURE 25.3

The rate of rise in alveolar tension of several anesthetic agents.

anesthesia, that is, after patients become unconscious. As body tissues become saturated with anesthetic molecules, blood returning to the lung will have increasingly high anesthetic tension, and the alveolar–arterial tension gradient will be reduced. Since the gradient controls the rate of diffusion across the alveolar capillary membrane, uptake is also reduced and the rate of rise of the alveolar tension of anesthetic is accelerated.

Effect of Solubility of Various Agents

The inhalational anesthetics have distinctly different solubility (affinity) characteristics in blood as well as in other tissues. These solubility differences are usually expressed as coefficients and indicate the number of volumes of a particular agent distributed in one phase, as compared with another, when the partial pressure is at equilibrium (Table 25.3). For example, isoflurane has a blood-to-gas partition coefficient (often referred to as the Ostwald solubility coefficient) of approximately 1.4. Thus, when the partial pressure has reached equilibrium, blood will contain 1.4 times as much isoflurane as an equal volume of alveolar air. The volume of the various anesthetics required to saturate blood is similar to that needed to saturate other body tissues (Table 25.3); that is, the blood–tissue partition coefficient is usually not more than 4 (that of adipose tissue is higher).

The solubility of anesthetic agents is a major factor for the rate of induction of anesthesia, or the time required to establish a level of unconsciousness adequate for surgery. Agents with limited plasma solubility and a low rate of uptake (e.g., N_2O , cyclopropane, sevoflurane, and desflurane) will equilibrate rapidly with tissues. For an agent that is highly soluble in plasma (e.g., methoxyflurane), the rate of rise of alveolar tension to the inspired level and the equilibration of the gas with brain will be delayed by a higher initial uptake into plasma from the alveoli. This phenomenon is often counterintuitive to students. However, with gases, partial pressure is the controlling factor for equilibration between tissues, and even though uptake is high, partial

pressure in the tissues and lung rises slowly, as large quantities of a highly soluble gas must be accumulated to establish the desired tension (Henry's law).

To illustrate the effect of solubility on the rate of induction of anesthesia, we can consider a situation in which individual agents are delivered to patients at their equivalent MAC values. Under these conditions, regardless of the agent being employed, a similar level of anesthesia will be achieved. In contrast, induction rates, illustrated as the time required for the alveolar tension to rise to the inspired level (Fig. 25.3), can be seen to be quite different. A patient receiving a MAC of N_2O , desflurane, or sevoflurane will be unconscious within 3 minutes. However, halothane, enflurane, and isoflurane, which have significant blood and tissue solubilities, will require at least 30 minutes before surgical anesthesia is established. Methoxyflurane, a highly soluble agent, requires several hours and may be clinically impractical if administered in this way.

Effect of Pulmonary Perfusion

The rate of pulmonary perfusion (in healthy individuals, essentially equivalent to the cardiac output) also affects the rate of induction of anesthesia. Since more blood will pass through the pulmonary capillary bed when the cardiac output is high, it follows that a greater total transfer of any anesthetic agent across the alveolus will

TABLE 25.3 Partition Coefficients of Some Anesthetic Gases at 37° C

Anesthetic Gas	Blood/Gas	Tissue/Blood
Cyclopropane	0.41	1.16 muscle 0.76 brain
Desflurane	0.42	2.00 muscle 1.30 brain
Nitrous oxide	0.47	1.15 muscle 1.06 brain
Sevoflurane	0.69	3.10 muscle 1.70 brain
Isoflurane	1.40	4.00 muscle 2.60 brain
Enflurane	1.80	1.70 muscle 1.45 brain
Halothane	2.30	3.40 muscle 3.50 brain (white) 2.30 brain (gray)
Diethyl ether	12.10	2.60 liver 1.14 brain 0.98 muscle
Methoxyflurane	12.00	2.30 brain (white) 1.70 brain (gray) 1.30 muscle

Adapted from Eger EI II (ed.). *Anesthetic Uptake and Action*. Baltimore: Williams & Wilkins, 1974:82.

occur in these conditions. Also, tissues normally receiving a smaller proportion of the total cardiac output receive a greater amount when cardiac output is high and will accumulate a larger proportion of the anesthetic crossing the alveolar membrane. Ultimately, greater uptake will slow the rate of rise of the alveolar tension–time curve, and anesthetic induction with an individual agent may be slower when the cardiac output and perfusion of the lung are high. In low cardiac output states, the reverse is true. The rate of uptake will be lower, and the alveolar tension will rise toward the inspired tension more quickly. To minimize the effect of cardiac output on the rate of induction of anesthesia, agents of lower solubility would be preferred clinically.

Effect of the Rate of Ventilation and Inspired Gas Concentration

Frequently it is desirable to overcome the slow rate of rise of alveolar tension associated with such factors as the high blood solubility of some anesthetics and increased pulmonary blood flow. Since both of these factors retard tension development by increasing the uptake of anesthetic, the most effective way to alleviate the problem is to accelerate the input of gas to the alveoli. A useful technique to increase the input of anesthetic to the lung is to elevate the minute alveolar ventilation. This maneuver, which causes a greater quantity of fresh anesthetic gas to be delivered to the patient per unit of time, is most effective with highly soluble agents (Fig. 25.4).

Increasing the inspired tension of an anesthetic gas above the maintenance tension (i.e., near the MAC value) is also an effective means of quickly establishing effective alveolar tension. This maneuver, frequently referred to as overpressure, parallels the concept of loading dose. As the desired depth of anesthesia or level of alveolar tension is achieved, the delivered tension of anesthetic must be returned to the maintenance (MAC) level to avoid overdosing the patient.

Other Factors Affecting the Alveolar Tension of Anesthetic Agents

Special factors influence the rate of rise of the alveolar tension to the inspired level when anesthetics are delivered in high concentration. These factors particularly significant when N_2O is used, since it is often required in concentrations exceeding 25% in the inspired air.

Concentration Effect

When anesthetics are delivered in high concentration, the alveolar tension will rise rapidly. Thus, if 75% N_2O is being delivered in the inspired air, the 75% tension in blood will be established more quickly than if 40% N_2O were being inhaled and a 40% N_2O tension were desired in blood. This phenomenon is illustrated in

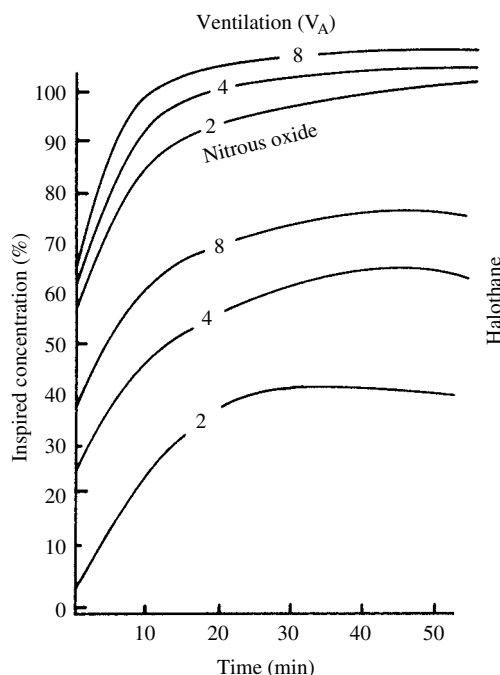


FIGURE 25.4

The alveolar rate of rise toward the inspired concentration (F_A/F_I) is accelerated by an increase in alveolar ventilation from 2 to 4 and from 4 to 8 liters per minute (constant cardiac output). The increase is greatest with the more soluble agent, halothane, and smaller with the least soluble anesthetic, nitrous oxide. (Reprinted with permission from Eger II [ed.]. *Anesthetic Uptake and Action*. Baltimore: Williams & Wilkins, 1974.)

Figure 25.5. An explanation is that when high inspired tensions of anesthetics are used, particularly if they are highly soluble, a large uptake from the alveoli will occur. Consequently, the lung volume may tend to shrink, causing negative pressure. However, the shrinkage is opposed by the pulling in of fresh gases from nonrespiratory conducting airway passages between inspirations, thus effectively increasing the total ventilation. Since greater uptake will occur with 75% N_2O than with 40%, the effect will be greater at higher inspired anesthetic tensions.

Second Gas Effect

The alveolar tension of other anesthetic gases also rises more rapidly (second gas effect) when an anesthetic such as N_2O is present in high concentration. These gases are also subject to the increased inflow (pulling in of fresh gases) as N_2O is taken up into the blood.

Diffusion Hypoxia

Diffusion hypoxia may be encountered at the end of an anesthetic administration with N_2O . The mechanism

underlying diffusion hypoxia is essentially the reverse of the concentration effect; that is, when anesthetic administration is stopped, large volumes of N_2O move from the blood into the alveolus, diluting oxygen and expanding lung expiratory volume. To avoid diffusion hypoxia, the anesthesiologist may employ 100% oxygen rather than room air after discontinuing administration of the anesthetic gas mixture.

Halogenated Hydrocarbon Anesthetics

Sevoflurane, desflurane, enflurane, isoflurane, halothane, and methoxyflurane are considered to be quite potent halogenated hydrocarbon anesthetics, since they produce surgical levels of anesthesia at low inspired partial pressures. None of the halogenated hydrocarbons, however, possess all of the pharmacological properties that are considered desirable for an anesthetic agent, so they are often given with other anesthetics and adjunctive drugs to provide effective and safe anesthetic management. The use of these drug combinations is referred to as balanced anesthesia.

Balanced Anesthesia with Inhalational Anesthetic Agents

An anesthetic plan based on the concept of balanced anesthesia may proceed as follows. First, since anesthetic partial pressure for an inhalational agent in the brain is not attained rapidly, patients are usually anesthetized with an IV agent. A bolus of an IV anesthetic provides unconsciousness long enough to establish the anesthetic brain tension of most of the inhalational drugs. Second, a supplemental analgesic (i.e., an opioid or the inhalational gas N_2O) is required because halogenated hydrocarbons exhibit varying and often inadequate degrees of analgesia, so patients may respond to strongly noxious surgical manipulations with movement and reflex cardiovascular changes. Third, since the neuromuscular

blockade provided by the halogenated hydrocarbons is incomplete, neuromuscular blocking agents, such as succinylcholine or the curariform drugs, must be used to provide paralysis adequate for surgical access. Fourth, the anesthetic plan is also designed to minimize any undesirable cardiovascular and respiratory responses to these drugs. This includes using drug combinations that minimize the dose of the halogenated hydrocarbon. For example, N_2O 25 to 40%, which by itself produces minimal cardiovascular depression, is frequently used with about half of the MAC of a particular halogenated hydrocarbon; this tends to preserve cardiovascular stability. Since MACs are additive, unconsciousness is adequate when a combination of inhalational agents is used.

Halothane

Halothane (*Fluothane*) depresses respiratory function, leading to decreased tidal volume and an increased rate of ventilation. Since the increased rate does not adequately compensate for the decrease in tidal volume, minute ventilation will be reduced; plasma $PaCO_2$ rises, and hypoxic drive is depressed. With surgical anesthesia, spontaneous ventilation is inadequate, and the patient's ventilation must be controlled.

Halothane administration can result in a marked reduction in arterial blood pressure that is due primarily to direct myocardial depression, which reduces cardiac output. The fall in pressure is not opposed by reflex sympathetic activation, however, since halothane also blunts baroreceptor and carotid reflexes. Systemic vascular resistance is unchanged, although blood flow to various tissues is redistributed. Halothane also sensitizes the heart to the arrhythmogenic effect of catecholamines. Thus, maintenance of the patient's blood pressure with epinephrine must be done cautiously.

It is clinically significant that *cerebral* blood flow increases as a result of a direct relaxant action of halothane on cerebral vasculature. Intracranial pressure may rise to a level at which it can become dangerous in patients with intracranial pathology. Although the *coronary* arteries are dilated, coronary blood flow decreases because of the overall reduction in systemic blood pressure. Thus, the balance between myocardial perfusion and oxygen demand (which is reduced with halothane) should be taken into account for patients with cardiac disease.

Similar disturbances in intracranial pressure and coronary blood flow occur with most of the halogenated hydrocarbons. In addition, renal blood flow, filtration, and urine output decrease with the use of halothane. These changes also occur with other inhalational agents that reduce arterial blood pressure.

Halothane and all other halogenated hydrocarbons cause some relaxation of skeletal muscle. The relaxation is not adequate when muscle paralysis is a requirement of the operative procedure, but halothane's action will

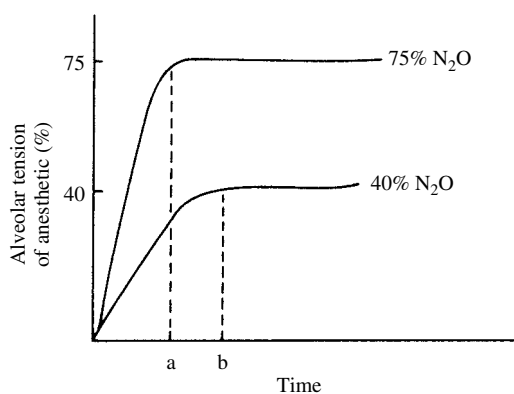


FIGURE 25.5

The effect of two concentrations of N_2O on the alveolar tension of anesthetic with time.

potentiate the effect of neuromuscular blocking drugs, reducing their dose requirement.

Although recovery from anesthesia does not rely on metabolic factors, halothane and many of the halogenated hydrocarbons undergo some biotransformation. Halothane is oxidized in the liver to trifluoroacetic acid, Br^- , and Cl^- . In the absence of oxygen, reductive intermediates of halothane metabolism may form and damage liver tissue. These intermediates have been implicated in a controversial syndrome of halothane hepatitis. This rare syndrome (1:35,000 anesthetics) is histologically indistinguishable from viral hepatitis. The likelihood of liver dysfunction increases with repeated administrations of halothane, and antibodies to hepatocytes are obtained from patients who develop liver dysfunction following halothane. It has been suggested that liver necrosis may be a hypersensitivity reaction, perhaps initiated by the reactive intermediates formed during halothane metabolism. It seems prudent to limit the use of halothane in patients with liver dysfunction that resulted from a previous exposure to the anesthetic.

Methoxyflurane

Methoxyflurane (*Penthrane*) is the most potent inhalational agent available, but its high solubility in tissues limits its use as an induction anesthetic. Its pharmacological properties are similar to those of halothane with some notable exceptions. For example, since methoxyflurane does not depress cardiovascular reflexes, its direct myocardial depressant effect is partially offset by reflex tachycardia, so arterial blood pressure is better maintained. Also, the oxidative metabolism of methoxyflurane results in the production of oxalic acid and fluoride concentrations that approach the threshold of causing renal tubular dysfunction. Concern for nephrotoxicity has greatly restricted the use of methoxyflurane.

Enflurane

Enflurane (*Ethrane*) depresses myocardial contractility and lowers systemic vascular resistance. In contrast to halothane, it does not block sympathetic reflexes, and therefore, its administration results in tachycardia. However, the increased heart rate is not sufficient to oppose enflurane's other cardiovascular actions, so cardiac output and blood pressure fall. In addition, enflurane sensitizes the myocardium to catecholamine-induced arrhythmias, although to a lesser extent than with halothane. Enflurane depresses respiration through mechanisms similar to halothane's and requires that the patient's ventilation be assisted.

Neuromuscular transmission is depressed by enflurane, resulting in some skeletal muscle paralysis. Although muscle relaxation is inadequate for many surgical procedures, the anesthetic enhances the action of neuromuscular blocking agents, thereby lowering the dose of the paralytic agent needed and minimizing side effects.

Deep anesthesia with enflurane is associated with the appearance of seizurelike electroencephalographic (EEG) changes. Occasionally frank tonic-clonic seizures are observed. Consequently, other inhalational agents are usually given to patients with preexisting seizure disorders.

Another concern associated with the use of enflurane is its biotransformation, which leads to increased plasma fluoride. Following lengthy procedures in healthy patients, fluoride may reach levels that result in a mild reduction in renal concentrating ability. Thus, enflurane should be used cautiously in patients with clinically significant renal disease.

Isoflurane

Isoflurane (*Forane*) is a structural isomer of enflurane and produces similar pharmacological properties: some analgesia, some neuromuscular blockade, and depressed respiration. In contrast, however, isoflurane is considered a particularly safe anesthetic in patients with ischemic heart disease, since cardiac output is maintained, the coronary arteries are dilated, and the myocardium does not appear to be sensitized to the effects of catecholamines. Also, blood pressure falls as a result of vasodilation, which preserves tissue blood flow. Isoflurane causes transient and mild tachycardia by direct sympathetic stimulation; this is particularly important in the management of patients with myocardial ischemia.

Unlike enflurane, isoflurane does not produce a seizurelike EEG pattern. Furthermore, the metabolic transformation of isoflurane is only one-tenth that of enflurane, so fluoride production is quite low. Among the halogenated hydrocarbons, isoflurane is one of the most popular, since it preserves cardiovascular stability and causes a low incidence of untoward effects.

Desflurane

Desflurane (*Suprane*) shares most of the pharmacological properties of isoflurane. Desflurane has low tissue and blood solubility compared with other halogenated hydrocarbons, and its anesthetic partial pressure is thus established more rapidly. Recovery is similarly prompt when the patient is switched to room air or oxygen. Desflurane's popularity for outpatient procedures stems from its rapid onset and prompt elimination from the body by exhalation. A disadvantage is that desflurane irritates the respiratory tract; thus, it is not preferred for induction of anesthesia using an inhalational technique. However, desflurane may be used to maintain anesthesia after induction with an alternative IV or inhalational agent, preserving the advantage of rapid recovery.

Desflurane, like other halogenated hydrocarbon anesthetics, causes a decrease in blood pressure. The reduced pressure occurs primarily as a consequence of decreased vascular resistance, and since cardiac output is well maintained, tissue perfusion is preserved.

Desflurane stimulates the sympathetic nervous system and causes abrupt transient tachycardia during induction or as the concentration of the agent is raised to meet the patient's changing needs.

Desflurane causes an increase in the rate of ventilation, a decrease in tidal volume, and a decrease in minute volume as inspired concentrations only slightly exceed 1 MAC. Thus should anesthesiologists require desflurane to be administered near or above MAC levels, patients are likely to have marked reductions in PCO_2 .

Sevoflurane

Sevoflurane (*Ultane*) is the most recently introduced inhalation anesthetic. It has low tissue and blood solubility, which allows for rapid induction and emergence and makes it useful for outpatient and ambulatory procedures. It has the advantage of not being pungent, a characteristic that permits a smooth inhalation induction, and is particularly useful in pediatric anesthesia.

Hypotension is produced by sevoflurane as systemic vasodilation occurs and cardiac output decreases. Since it does not directly produce tachycardia, it is a useful alternative to consider in patients with myocardial ischemia. However, a concern for reflex-induced tachycardia remains.

Sevoflurane undergoes hepatic biotransformation (about 3% of the inhaled dose), and it is somewhat degraded by conventional CO_2 absorbents. The degradation product from the absorbent has been reported to be nephrotoxic, although the report is controversial and not substantiated by more recent studies. Sevoflurane's actions on skeletal muscle and on vascular regulation within the CNS are similar to those described for the other halogenated hydrocarbon anesthetics.

Nonhalogenated Inhalational Anesthetics

In contemporary surgical settings, the only useful nonhalogenated inhalational anesthetic is N_2O . Earlier agents, ether and cyclopropane, have fallen out of favor, since they present a serious safety hazard due to their flammability and explosiveness. They remain interesting from a historical point of view, since they were among the first developed.

Nitrous Oxide: An Inhalational Gas

N_2O (commonly called laughing gas) produces its anesthetic effect without decreasing blood pressure or cardiac output. Although it directly depresses the myocardium, cardiac depression is offset by an N_2O -mediated sympathetic stimulation. Likewise, respiration is maintained. Tidal volume falls, but minute ventilation is supported by a centrally mediated increase in respiratory rate. However, since the respiratory depressant effect of N_2O are synergistic with drugs such as the opi-

oids and benzodiazepines, N_2O should not be considered benign.

Deep levels of anesthesia are unattainable, even when using the highest practical concentrations of N_2O (N_2O 60–80% with oxygen 40–20%). Although unconsciousness occurs at these inspired levels, patients exhibit signs of CNS excitation, such as physical struggling and vomiting. If the airway is unprotected, vomiting may lead to aspiration pneumonitis, since the protective reflexes of the airway are depressed.

On the other hand, lower inspired concentrations (25–40%) of N_2O produce CNS depression without excitatory phenomena and are more safely used clinically. CNS properties of low inspired tension of N_2O include periods of waxing and waning consciousness, amnesia, and extraordinarily effective analgesia. N_2O 25% produces the gas's maximum analgesic effect. With this concentration, responses to painful surgical manipulations are blocked as effectively as they would be with a therapeutic dose of morphine. Such low inspired concentrations of N_2O are used in dentistry and occasionally for selected painful surgical procedures (i.e., to relieve the pain of labor). Since the tissue solubility of N_2O is low, the CNS effects are rapid in onset, and recovery is prompt when the patient is returned to room air or oxygen.

The most common use of N_2O is in combination with the more potent volatile anesthetics. It decreases the dosage requirement for the other anesthetics, thus lowering their cardiovascular and respiratory toxicities. For example, an appropriate anesthetic maintenance tension for N_2O and halothane would be N_2O 40% and halothane 0.5%. With this combination in a healthy patient, anesthesia is adequate for major surgery, and the dose-dependent cardiac effects of halothane are reduced.

MECHANISM OF ANESTHETIC ACTION

Among the earliest proposals to explain the mechanism of action of anesthetics is the concept that they interact physically rather than chemically with lipophilic membrane components to cause neuronal failure. However, this concept proposes that all anesthetics interact in a common way (the unitary theory of anesthesia), and it is being challenged by more recent work demonstrating that specific anesthetics exhibit selective and distinct interactions with neuronal processes and that those interactions are not easily explained by a common physical association with membrane components. Proposals for the production of anesthesia are described next.

Anesthesia from Physical Interactions with Lipophilic Membrane Components

The idea that a physical interaction is important stems from experimental observations made in the late nineteenth and early twentieth centuries, when it was recognized that noble gases such as xenon, which do not

chemically interact with tissues, produce unconsciousness. Also, anesthesia produced at ambient atmospheric pressure can be attenuated by physically raising the pressure to 100 atm, a phenomenon known as pressure reversal. Finally, a clear correlation exists between anesthetic potency and the physical parameter lipid solubility, suggesting that anesthesia may be produced when anesthetics physically dissolve into the cell membrane's lipid bi-phase (Meyer Overton rule). Such a correlation is shown in Fig. 25.6, where anesthetic potency is expressed as MAC and lipid solubility is estimated as the oil-gas partition.

Membrane conformational changes are observed on exposure to anesthetics, further supporting the importance of physical interactions that lead to perturbation of membrane macromolecules. For example, exposure of membranes to clinically relevant concentrations of anesthetics causes membranes to expand beyond a critical volume (critical volume hypothesis) associated with normal cellular function. Additionally, membrane structure becomes disorganized, so that the insertion of anesthetic molecules into the lipid membrane causes an increase in the mobility of the fatty acid chains in the phospholipid bilayer (membrane fluidization theory) or prevent the interconversion of membrane lipids from a gel to a liquid form, a process that is assumed necessary for normal neuronal function (lateral phase separation hypothesis).

Anesthesia from Selective Interactions of Anesthetics with Cellular Components

While current observations do not rule out that anesthetics may require a hydrophobic environment near the site of their action, they do suggest that various agents may also have distinct interactions with tissues. For example, enantiomers of newer agents have selec-

tive and unique actions, even though they have identical physical properties; for example, stereoisomers of isoflurane are differentially potent but have identical oil-gas partition coefficients.

Contemporary research has shown that at clinically relevant concentrations, various anesthetics interact specifically with different components of the GABA_A-receptor-chloride ionophore and enhance chloride conductance, some directly and others by enhancing the action of GABA. Inhalational agents directly activate the chloride channel as well as facilitate the action of GABA, while barbiturates, propofol, benzodiazepines, and etomidate primarily enhance the action of GABA by interacting with specific receptor sites (Fig. 25.7). Also, anesthetics enhance other processes known to inhibit neuronal function, such as the glycine receptor-gated chloride channel. A smaller number of anesthetics, including ketamine, N₂O, and xenon, produce neuronal inhibition by antagonizing excitatory neuronal transmission mediated via the *N*-methyl-D-aspartic acid (NMDA) receptor. In addition, some inhalational drugs activate K⁺ channels and so contribute to hyperpolarization and reduced neuronal excitability; they also inhibit the function of the protein complex involved in neurotransmitter release.

Clearly much must be explained of the complex changes in the CNS that eventually produce unconsciousness. Although physical interactions of anesthetics with hydrophobic membrane components may lead to conformational changes that alter neuronal function, specific interactions at critical receptors and ion channels are also likely to contribute to anesthesia. Thus, structurally and pharmacologically diverse anesthetic drugs produce unconsciousness through qualitatively different mechanisms and through actions occurring at anatomically distinct sites in the nervous system.

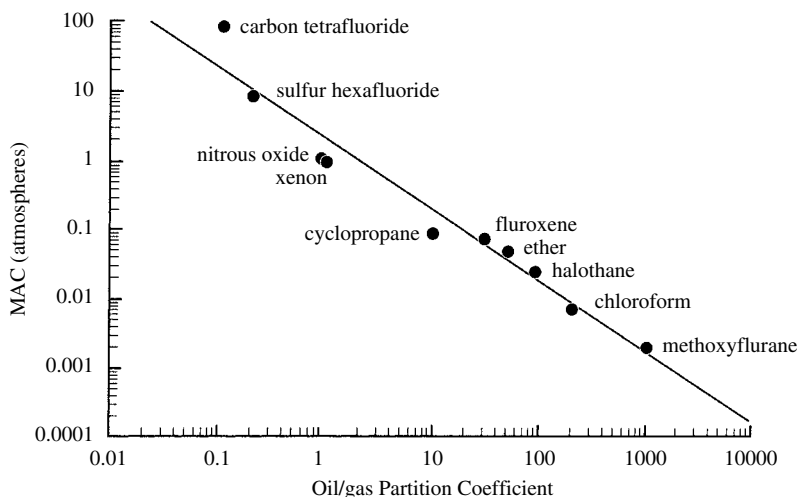
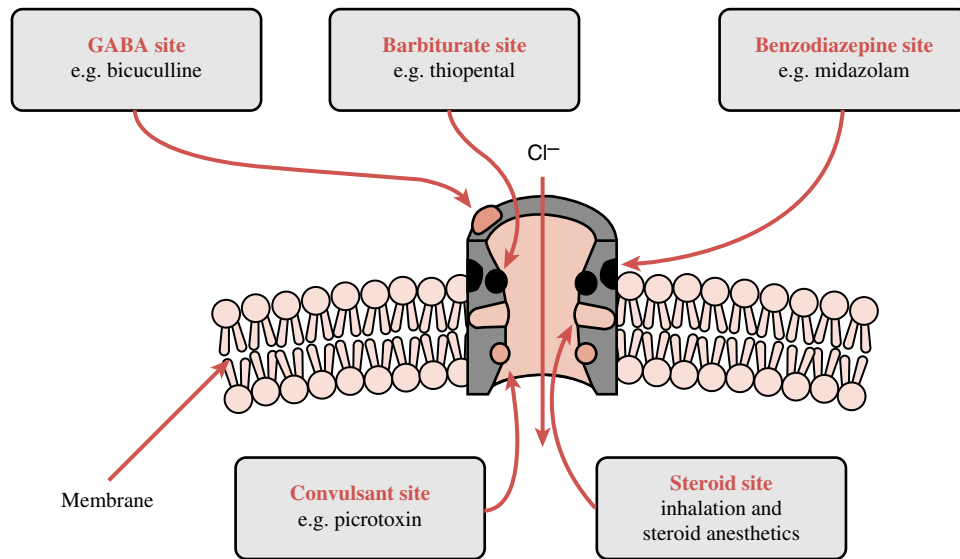


FIGURE 25.6

A comparison of the minimum alveolar concentration (MAC) with the oil-gas partition coefficient of several inhalational anesthetic agents.

**FIGURE 25.7**

The GABA_A-receptor–chloride ionophore sites of drug action.

Study QUESTIONS

- A patient whose anesthesia is being managed only with isoflurane (Forane) delivered at an inspired concentration near the MAC occasionally moves and exhibits facial grimacing, apparently in response to surgical manipulation of the bowel. These responses are

 - Natural consequences of physical manipulations that induce noxious sensory input to the CNS
 - An indication that neuromuscular blocking agents should be administered without delay
 - Not likely to be blocked by coadministering an analgesic drug such as morphine
 - Signs suggesting that the patient should be given twice the MAC of isoflurane
 - Not avoidable because the bowel is unusually sensitive to physical manipulation.
- A hypotensive patient suspected of having internal bleeding is given a dose lower than the usual amount of an intravenous anesthetic. An acceptable level of anesthesia occurs. How is it possible to achieve anesthesia in this patient with a dose of anesthetic that may be inadequate in a normotensive patient with adequate blood volume?

 - Enzymatic activity of hepatic enzymes is compromised when blood pressure is low.
 - More anesthetic appears in the brain and redistribution of the intravenous drug to tissues with reduced blood flow is compromised when hemorrhagic shock occurs.
 - The diffusion of lipid-soluble drugs through the blood-brain barrier is enhanced.
 - Tissues with a characteristically high blood flow per unit mass receive less blood and less anesthetic when blood volume is low.
 - Anesthetics bind more readily to tissue receptors when hypotension and poor oxygenation occur.
- With which hypothetical anesthetic would you expect anesthetic partial pressure to be achieved relatively quickly?

 - An agent that is highly soluble in blood and other body tissues
 - An agent with a low MAC (in range less than 1% in the inspired air)
 - An agent with a high Ostwald solubility coefficient
 - An agent whose rate of rise of partial pressure in the lung is influenced minimally by uptake into the blood.
 - An agent supplied as a gas rather than one supplied as a volatile liquid
- Remifentanyl (Ultiva) has recently gained popularity as a high-dose opioid anesthesia because

 - It induces anesthesia in patients faster than any other drug

- (B) Phenylpiperidine-type opioids releases histamine from mast cells
- (C) It is metabolized by nonspecific esterases in red blood cells and other tissues
- (D) It has a long duration of action following intravenous infusion
- (E) It does not produce chest wall rigidity
5. Patients with coronary artery disease are particularly challenging for anesthesia, since alterations in vascular responsiveness and myocardial function may put them at risk. In this respect, which statement correctly describes the cardiovascular action of an agent or agents that should be taken into account when planning anesthesia for such patients?
- (A) All halogenated hydrocarbon inhalational anesthetics sensitize the myocardium to catecholamine-induced cardiac arrhythmias.
- (B) Halogenated hydrocarbon inhalational agents reduce cardiac output equally well.
- (C) Sevoflurane (Ultane) directly stimulates sympathetic function.
- (D) Reflex sympathetic stimulation is a major component of halothane's (Fluothane) cardiovascular profile.
- (E) Several halogenated hydrocarbons produce vascular relaxation to reduce blood pressure.
6. The mechanism of anesthesia remains an active area of research. Which statement best describes significant developments in this area of scientific investigation?
- (A) Anesthetics are physically attracted to the aqueous phase of neuronal membranes.
- (B) Anesthesia is associated with interactions of the agents with a single unique site on the GABA_A receptor.
- (C) Anesthesia ultimately occurs as Cl⁻ moves out of neuronal cells, an action that makes the cells less excitable.
- (D) Although some exceptions occur, a correlation between anesthetic potency and their oil-water partition coefficient suggested a unitary hypothesis for the production of anesthesia.
- (E) Enantiomers of inhalational agents provide support for the Meyer Overton rule.

ANSWERS

1. **A.** Unless supplemented with strong analgesic drugs such as opioids, most general anesthetics allow reflex reactions to painful stimuli, which may include movement and autonomic reflex changes. Even though these reflex changes occur, if adequately anesthetized, patients will not experience the noxious stimulus. To give this patient a neuromuscular blocking agent without initially evaluating the adequacy of anesthesia would be a mistake. A lawsuit is almost certain, should the patient be inad-

equately anesthetized and complain postoperatively of being aware but paralyzed. If it is determined that the patient is receiving adequate anesthesia (i.e., evaluate the delivery of gas, and check other reflexes such as corneal), the use of a neuromuscular blocking drug may be acceptable if movement is interfering with the procedure. Morphine may be a reasonable supplement to anesthetic management to inhibit reflex reactions to noxious stimuli. Raising the inspired concentration of isoflurane may further blunt reflex reactions to noxious stimuli. However, it may not be a wise choice, since multiples of MAC may cause greater instability of physiological functions (i.e. cardiovascular function). Use a balanced anesthetic approach with adjunctive agents. The gut is quite responsive to noxious insult, but the reflex responses are still inhibited with proper analgesics, so muscular movement is avoidable.

2. **B.** Perfusion of the brain is preserved when hemorrhage occurs. Thus, a greater proportion of the initial dose of anesthetic should appear in the brain, and a dose smaller than what is needed for a normovolemic patient is all that is required. Also, since flow to tissues associated with redistribution of the drug and termination of anesthesia is compromised, anesthesia should be deep and extended. Titrate this patient to a safe level of effect. While poor perfusion of the liver may reduce the exposure of drugs to metabolic enzymes, most intravenous anesthetics rely very little on hepatic clearance to terminate the anesthetic effect when a single bolus is administered. Furthermore, the question implies a direct influence of blood pressure on the efficiency of hepatic enzymes, and there is no evidence to support such a contention. Option C is not true. The opposite of option D is true. No evidence exists that binding of anesthetics is altered by these conditions.
3. **D.** Anesthetics with low blood and tissue solubility require minimal uptake from the lung, as alveolar partial pressure equilibrates with tissue. Remember, alveolar partial pressure is the driving force to establish tension gradients throughout the body. Thus, when uptake is low and alveolar tension rises quickly, blood and brain (which receives a high blood flow) equilibrate with gaseous agents quickly, and anesthesia is induced relatively rapidly. A gas that is highly soluble in tissues requires a greater accumulation from the lung before partial pressure equilibria are attained, since with greater uptake the rate of rise of the alveolar tension to the inspired level is slower. Although a relationship exists between MAC and blood solubility with respect to anesthetic concentration in the tissues, the association suggested by choice B is opposite the expectation. Consider the implications of the Meyer Overton rule. An agent with a high Ostwald solubil-

ity coefficient is one of the more soluble agents in tissue, so the explanation of option A applies.

Option E has no apparent bearing on the rate of rise of the alveolar partial pressure in brain, alveolus, or any other tissue.

4. **C.** Remifentanyl has become popular as a component drug in the technique of total intravenous anesthesia as a consequence of this feature. It is distribution of blood to the brain, not specific pharmacological properties, that primarily controls the rate of induction of anesthesia with IV agents. Phenylpiperidines as a class of opioids are less likely to produce histamine release. Moreover, histamine release may complicate anesthetic management (e.g. bronchoconstriction and hypotension), so if it were an action of remifentanyl it would be a negative feature. Remifentanyl's duration of action is short because it is rapidly metabolized. Chest wall rigidity is associated with high doses of phenylpiperidine opioids in particular, and no evidence suggests that remifentanyl would be any less likely to cause such an effect.
5. **E.** Reduced peripheral vascular resistance occurs with most halogenated hydrocarbons, and reflex tachycardia may be a concern. Halothane may be the clearest exception, since there appears to be a balance between relaxation and constrictor influences in various vascular beds with this agent so that total peripheral resistance changes very little. Halothane is the agent of concern when sensitization of the myocardium to catecholamine-induced arrhythmias may be important, such as during incidences of hypercapnia. Sevoflurane does not directly influence sympathetic function. However, reflex tachycardia can occur. Reflex sympathetic

stimulation is blocked by halothane. In fact, this may be an advantage of the drug in physiologically risky patients when swings in blood pressure are likely to be frequent.

6. **D.** Although few contend that a unitary hypothesis will explain anesthesia, the Meyer Overton rule was among the first explanations provided by the scientific community. The correlation remains significant, as it suggests that sites of action for various anesthetics may reside near (or the agent must pass through) hydrophobic tissue components. Also, physical disruption of membrane function may yet be found to play a role for at least some agents. Option A is the reverse of the true interaction. Several sites on the GABA receptor complex may be involved. Cl⁻ moves inward to cause cells to become less excitable. Enantiomers, which have nearly identical physical properties but different potencies, challenge the Meyer Overton rule.

SUPPLEMENTAL READING

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CASE Study Bradycardia and β -Blockers

A 77-year-old man is admitted to the hospital for a coronary artery bypass. He has been treated with a β -blocker (Tenormin 100 mg per day), which he took every morning. He is induced with propofol 1 mg/kg, fentanyl 5 μ g/kg and vecuronium 8 mg for muscle relaxation. After 3 minutes a decreasing heart rate becomes a worry for the anesthesiologist. The heart rate continues to fall until it reaches 38 BPM. At this point the patient's blood pressure is 80/60 and the anesthesiologist gives atropine 0.4 mg and ephedrine 10 mg. This treatment results in a stable patient. What effects were most likely produced by the anesthesia procedure? Could this have been avoided?

ANSWER: This feature of bradycardia is typical of patients who take β -blockers, which should be continued so they result ultimately in better anesthetic management. The drugs given could have been modified (i.e., etomidate instead of propofol, which does not raise or may cause a slower heart rate). The potent opioids in the fentanyl family all cause vagal transmitted bradycardia. The muscle relaxant vecuronium (norcuron) has no effect on heart rate and could have been replaced by pancuronium, which has a vagolytic effect and will counter bradycardia in the usual induction bolus doses.