CHAPTER

8

Inhalation Anesthetics

KEY CONCEPTS

1. The greater the uptake of anesthetic agent, the greater the difference between inspired and alveolar concentrations, and the slower the rate of induction.
2. Three factors affect anesthetic uptake: solubility in the blood, alveolar blood flow, and the difference in partial pressure between alveolar gas and venous blood.
3. Low-output states predispose patients to overdosage with soluble agents, as the rate of rise in alveolar concentrations will be markedly increased.
4. Many of the factors that speed induction also speed recovery: elimination of rebreathing, high fresh gas flows, low anesthetic-circuit volume, low absorption by the anesthetic circuit, decreased solubility, high cerebral blood flow, and increased ventilation.
5. The unitary hypothesis proposes that all inhalation agents share a common mechanism of action at the molecular level. This is supported by the observation that the anesthetic potency of inhalation agents correlates directly with their lipid solubility (Meyer–Overton rule). There is an ongoing debate as to the mechanism of anesthetic action. Anesthetic interactions at specific protein ion channels, as well as more nonspecific membrane effects, may combine to produce the anesthetized state.
6. The minimum alveolar concentration (MAC) is the alveolar concentration of an inhaled anesthetic that prevents movement in 50% of patients in response to a standardized stimulus (eg, surgical incision).
7. Prolonged exposure to anesthetic concentrations of nitrous oxide can result in bone marrow depression (megaloblastic anemia) and even neurological deficiencies (peripheral neuropathies).
8. Halothane hepatitis is extremely rare (1 per 35,000 cases). Patients exposed to multiple halothane anesthetics at short intervals, middle-aged obese women, and persons with a familial predisposition to halothane toxicity or a personal history of toxicity are considered to be at increased risk. Desflurane and isoflurane undergo much less metabolism than halothane, resulting in fewer of the metabolite protein adducts that lead to immunologically mediated hepatic injury.
9. Isoflurane dilates coronary arteries, but is not nearly as potent a dilator as nitroglycerin or adenosine. Dilation of normal coronary arteries could theoretically divert blood away from fixed stenotic lesions.
10. The low solubility of desflurane in blood and body tissues causes a very rapid induction of and emergence from anesthesia.

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11 Rapid increases in desflurane concentration lead to transient but sometimes worrisome elevations in heart rate, blood pressure, and catecholamine levels that are more pronounced than occur with isoflurane, particularly in patients with cardiovascular disease.

12 Nonpungency and rapid increases in alveolar anesthetic concentration make sevoflurane an excellent choice for smooth and rapid inhalation inductions in pediatric and adult patients.

Nitrous oxide, chloroform, and ether were the first universally accepted general anesthetics. Methoxyflurane and enflurane, two potent halogenated agents, were used for many years in North American anesthesia practice. Methoxyflurane was the most potent inhalation agent, but its high solubility and low vapor pressure yielded longer inductions and emergences. Up to 50% of it was metabolized by cytochrome P-450 (CYP) enzymes to free fluoride (F^-), oxalic acid, and other nephrotoxic compounds. Prolonged anesthesia with methoxyflurane was associated with a vasopressin-resistant, high-output, renal failure that was most commonly seen when F^- levels increased to greater than 50 μmol/L. Enflurane has a nonpungent odor and is nonflammable at clinical concentrations. It depresses myocardial contractility. It also increases the secretion of cerebrospinal fluid (CSF) and the resistance to CSF outflow. During deep anesthesia with hypocarbia electroencephalographic changes can progress to a spike-and-wave pattern producing tonic–clonic seizures. Because of these concerns, methoxyflurane and enflurane are no longer used.

Five inhalation agents continue to be used in clinical anesthesiology: nitrous oxide, halothane, isoflurane, desflurane, and sevoflurane.

The course of a general anesthetic can be divided into three phases: (1) induction, (2) maintenance, and (3) emergence. Inhalation anesthetics, such as halothane and sevoflurane, are particularly useful in the induction of pediatric patients in whom it may be difficult to start an intravenous line. Although adults are usually induced with intravenous agents, the nonpungency and rapid onset of sevoflurane make inhalation induction practical for them as well. Regardless of the patient's age, anesthesia is often maintained with inhalation agents. Emergence depends primarily upon redistribution from the brain and pulmonary elimination of these agents.

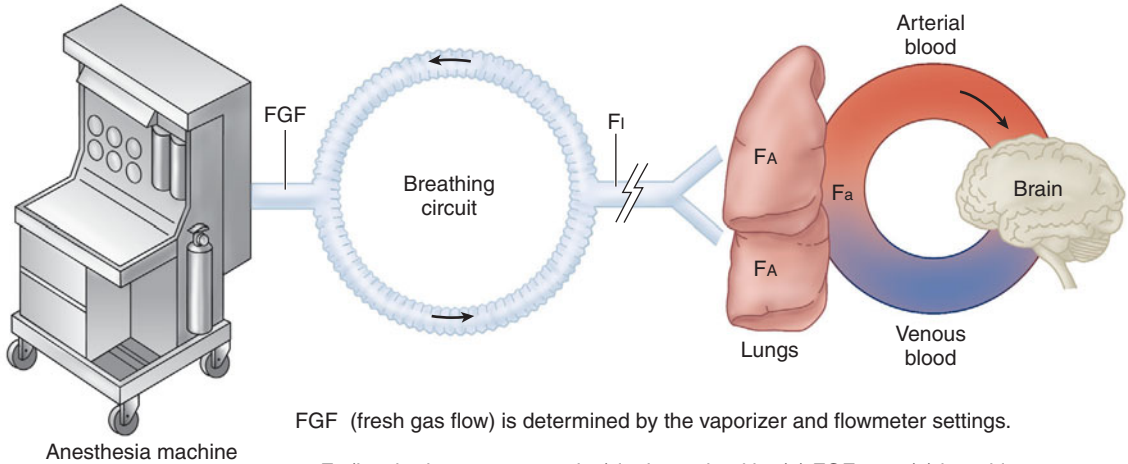
Because of their unique route of administration, inhalation anesthetics have useful pharmacological properties not shared by other anesthetic agents. For instance, administration via the pulmonary circulation allows a more rapid appearance of the drug in arterial blood than intravenous administration.

Pharmacokinetics of Inhalation Anesthetics

Although the mechanism of action of inhalation anesthetics is complex, likely involving numerous membrane proteins and ion channels, it is clear that producing their ultimate effect depends on attainment of a therapeutic tissue concentration in the central nervous system (CNS). There are many steps in between the anesthetic vaporizer and the anesthetic's deposition in the brain (**Figure 8–1**).

FACTORS AFFECTING INSPIRATORY CONCENTRATION (F_I)

The fresh gas leaving the anesthesia machine mixes with gases in the breathing circuit before being inspired by the patient. Therefore, the patient is not necessarily receiving the concentration set on the



FGF (fresh gas flow) is determined by the vaporizer and flowmeter settings.

FI (inspired gas concentration) is determined by (1) FGF rate; (2) breathing-circuit volume; and (3) circuit absorption.

FA (aveolar gas concentration) is determined by (1) uptake (uptake = λb/g x C(A-V) x Q); (2) ventilation; and (3) the concentration effect and second gas effect:
a) concentrating effect
b) augmented inflow effect

Fa (arterial gas concentration) is affected by ventilation/perfusion mismatching.

FIGURE 8–1 Inhalation anesthetic agents must pass through many barriers between the anesthesia machine and the brain.

vaporizer. The actual composition of the inspired gas mixture depends mainly on the fresh gas flow rate, the volume of the breathing system, and any absorption by the machine or breathing circuit. The higher the fresh gas flow rate, the smaller the breathing system volume, and the lower the circuit absorption, the closer the inspired gas concentration will be to the fresh gas concentration. Clinically, these attributes translate into faster induction and recovery times.

FACTORS AFFECTING ALVEOLAR CONCENTRATION (FA)

Uptake

If there were no uptake of anesthetic agent by the body, the alveolar gas concentration (FA) would rapidly approach the inspired gas concentration (FI). Because anesthetic agents are taken up by the pulmonary circulation during induction, alveolar concentrations lag behind inspired concentrations (FA/FI <1.0). The greater the uptake, the slower the rate of rise of the alveolar concentration and the lower the FA:FI ratio.

Because the concentration of a gas is directly proportional to its partial pressure, the alveolar partial pressure will also be slow to rise. The alveolar partial pressure is important because it determines the partial pressure of anesthetic in the blood and, ultimately, in the brain. Similarly, the partial pressure of the anesthetic in the brain is directly proportional to its brain tissue concentration, which determines clinical effect.

1 Therefore, the greater the uptake of anesthetic agent, the greater the difference between inspired and alveolar concentrations, and the slower the rate of induction.

TABLE 8–1 Partition coefficients of volatile anesthetics at 37°C.[1]

Agent	Blood/Gas	Brain/Blood	Muscle/Blood	Fat/Blood
Nitrous oxide	0.47	1.1	1.2	2.3
Halothane	2.4	2.9	3.5	60
Isoflurane	1.4	2.6	4.0	45
Desflurane	0.42	1.3	2.0	27
Sevoflurane	0.65	1.7	3.1	48

[1]These values are averages derived from multiple studies and should be used for comparison purposes, not as exact numbers.

2 Three factors affect anesthetic uptake: solubility in the blood, alveolar blood flow, and the difference in partial pressure between alveolar gas and venous blood.

Relatively soluble agents, such as nitrous oxide, are taken up by the blood less avidly than more soluble agents, such as halothane. As a consequence, the alveolar concentration of nitrous oxide rises faster than that of halothane, and induction is faster. The relative solubilities of an anesthetic in air, blood, and tissues are expressed as partition coefficients (Table 8–1). Each coefficient is the ratio of the concentrations of the anesthetic gas in each of two phases at steady state. Steady state is defined as equal partial pressures in the two phases. For instance, the blood/gas partition coefficient ($\lambda_{b/g}$) of nitrous oxide at 37°C is 0.47. In other words, at steady state, 1 mL of blood contains 0.47 as much nitrous oxide as does 1 mL of alveolar gas, even though the partial pressures are the same. Stated another way, blood has 47% of the capacity for nitrous oxide as alveolar gas. Nitrous oxide is much less soluble in blood than is halothane, which has a blood/gas partition coefficient at 37°C of 2.4. Thus, almost five times more halothane than nitrous oxide must be dissolved to raise the partial pressure of blood. The higher the blood/gas coefficient, the greater the anesthetic's solubility and the greater its uptake by the pulmonary circulation. As a consequence of this increased solubility, alveolar partial pressure rises more slowly, and induction is prolonged. Because fat/blood partition coefficients are greater than 1, blood/gas solubility is increased by postprandial lipidemia and is decreased by anemia.

The second factor that affects uptake is alveolar blood flow, which—in the absence of pulmonary shunting—is essentially equal to cardiac output. If the cardiac output drops to zero, so will anesthetic uptake. As cardiac output increases, anesthetic uptake increases, the rise in alveolar partial pressure slows, and induction is delayed. The effect of changing cardiac output is less pronounced for insoluble anesthetics, as so little is taken up regardless of alveolar blood flow. Low-output states predispose 3 patients to overdosage with soluble agents, as the rate of rise in alveolar concentrations will be markedly increased.

The final factor affecting uptake of anesthetic by the pulmonary circulation is the partial pressure difference between alveolar gas and venous blood. This gradient depends on tissue uptake. If anesthetics did not pass into organs such as the brain, venous and alveolar partial pressures would become identical, and there would be no pulmonary uptake. The transfer of anesthetic from blood to tissues is determined by three factors analogous to systemic uptake: tissue solubility of the agent (tissue/blood partition coefficient), tissue blood flow, and the difference in partial pressure between arterial blood and the tissue.

To better understand inhaled anesthetic uptake and distribution, tissues have been classified into four groups based on their solubility and blood flow (Table 8–2). The highly perfused vessel-rich group (brain, heart, liver, kidney, and endocrine organs) is

TABLE 8–2 Tissue groups based on perfusion and solubilities.

Characteristic	Vessel Rich	Muscle	Fat	Vessel Poor
Percentage of body weight	10	50	20	20
Percentage of cardiac output	75	19	6	0
Perfusion (mL/min/100 g)	75	3	3	0
Relative solubility	1	1	20	0

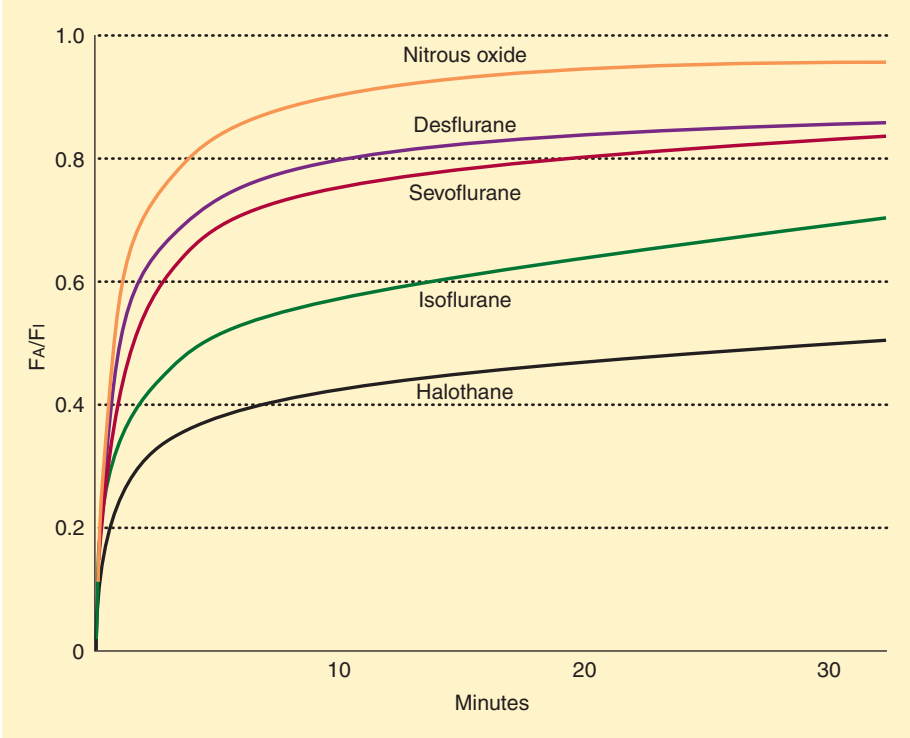


FIGURE 8–2 F_A rises toward F_I faster with nitrous oxide (an insoluble agent) than with halothane (a soluble agent). See Figure 8–1 for an explanation of F_A and F_I.

the first to encounter appreciable amounts of anesthetic. Moderate solubility and small volume limit the capacity of this group, so it is also the first to reach steady state (ie, arterial and tissue partial pressures are equal). The muscle group (skin and muscle) is not as well perfused, so uptake is slower. In addition, it has a greater capacity due to a larger volume, and uptake will be sustained for hours. Perfusion of the fat group nearly equals that of the muscle group, but the tremendous solubility of anesthetic in fat leads to a total capacity (tissue/blood solubility × tissue volume) that would take days to approach steady state. The minimal perfusion of the vessel-poor group (bones, ligaments, teeth, hair, and cartilage) results in insignificant uptake.

Anesthetic uptake produces a characteristic curve that relates the rise in alveolar concentration to time (Figure 8–2). The shape of this graph is determined by the uptakes of individual tissue groups (Figure 8–3). The initial steep rate of uptake is due to unopposed filling of the alveoli by ventilation. The rate of rise slows as the vessel-rich group—and eventually the muscle group—approach steady state levels of saturation.

Ventilation

The lowering of alveolar partial pressure by uptake can be countered by increasing alveolar ventilation. In other words, constantly replacing anesthetic taken up by the pulmonary bloodstream results in better maintenance of alveolar concentration. The effect of increasing ventilation will be most obvious in raising the F_A/F_I for soluble anesthetics, as they are more subject to uptake. Because the F_A/F_I very rapidly approaches 1.0 for insoluble agents, increasing ventilation has minimal effect. In contrast to the effect of anesthetics on cardiac output, anesthetics that depress spontaneous ventilation (eg, ether or

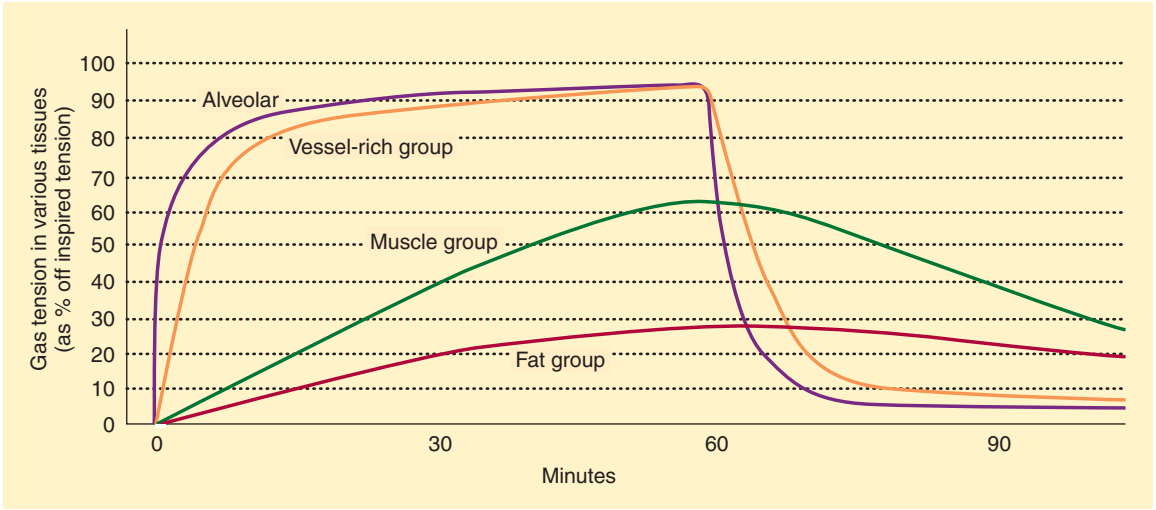


FIGURE 8–3 The rise and fall in alveolar partial pressure precedes that of other tissues. (Modified and reproduced, with permission, from Cowles AL et al: Uptake and distribution of inhalation anesthetic agents in clinical practice. Anesth Analg 1968;4:404.)

halothane) will decrease the rate of rise in alveolar concentration and create a negative feedback loop.

Concentration

The slowing of induction due to uptake from alveolar gas can be reduced by increasing the inspired concentration. Interestingly, increasing the inspired concentration not only increases the alveolar concentration, but also increases its rate of rise (ie, increases F_A/F_I), because of two phenomena (see Figure 8–1) that produce a so-called "concentrating effect." First, if 50% of an anesthetic is taken up by the pulmonary circulation, an inspired concentration of 20% (20 parts of anesthetic per 100 parts of gas) will result in an alveolar concentration of 11% (10 parts of anesthetic remaining in a total volume of 90 parts of gas). On the other hand, if the inspired concentration is raised to 80% (80 parts of anesthetic per 100 parts of gas), the alveolar concentration will be 67% (40 parts of anesthetic remaining in a total volume of 60 parts of gas). Thus, even though 50% of the anesthetic is taken up in both examples, a higher inspired concentration results in a disproportionately higher alveolar concentration. In this example, increasing the inspired concentration 4-fold results in a 6-fold increase in alveolar concentration. The extreme case is an inspired concentration of 100% (100 parts of 100), which, despite a 50% uptake, will result in an alveolar concentration of 100% (50 parts of anesthetic remaining in a total volume of 50 parts of gas).

The second phenomenon responsible for the concentration effect is the augmented inflow effect. Using the example above, the 10 parts of absorbed gas must be replaced by an equal volume of the 20% mixture to prevent alveolar collapse. Thus, the alveolar concentration becomes 12% (10 plus 2 parts of anesthetic in a total of 100 parts of gas). In contrast, after absorption of 50% of the anesthetic in the 80% gas mixture, 40 parts of 80% gas must be inspired. This further increases the alveolar concentration from 67% to 72% (40 plus 32 parts of anesthetic in a volume of 100 parts of gas).

The concentration effect is more significant with nitrous oxide, than with the volatile anesthetics, as the former can be used in much higher concentrations. Nonetheless, a high concentration of nitrous oxide will augment (by the same mechanism) not only its own uptake, but theoretically that of a concurrently administered volatile anesthetic. The concentration effect of one gas upon another is called the second gas effect, which is probably insignificant in the clinical practice of anesthesiology.

FACTORS AFFECTING ARTERIAL CONCENTRATION (Fa)

Ventilation/Perfusion Mismatch

Normally, alveolar and arterial anesthetic partial pressures are assumed to be equal, but in fact, the arterial partial pressure is consistently less than end-expiratory gas would predict. Reasons for this may include venous admixture, alveolar dead space, and nonuniform alveolar gas distribution. Furthermore, the existence of ventilation/perfusion mismatching will increase the alveolar–arterial difference. Mismatch acts as a restriction to flow: It raises the pressure in front of the restriction, lowers the pressure beyond the restriction, and reduces the flow through the restriction. The overall effect is an increase in the alveolar partial pressure (particularly for highly soluble agents) and a decrease in the arterial partial pressure (particularly for poorly soluble agents). Thus, a bronchial intubation or a right-to-left intracardiac shunt will slow the rate of induction with nitrous oxide more than with halothane.

FACTORS AFFECTING ELIMINATION

Recovery from anesthesia depends on lowering the concentration of anesthetic in brain tissue. Anesthetics can be eliminated by biotransformation, transcutaneous loss, or exhalation. Biotransformation usually accounts for a minimal increase in the rate of decline of alveolar partial pressure. Its greatest impact is on the elimination of soluble anesthetics that undergo extensive metabolism (eg, methoxyflurane). The greater biotransformation of halothane compared with isoflurane accounts for halothane's faster elimination, even though it is more soluble. The CYP group of isozymes (specifically CYP 2EI) seems to be important in the metabolism of some volatile anesthetics. Diffusion of anesthetic through the skin is insignificant.

4 The most important route for elimination of inhalation anesthetics is the alveolus. Many of the factors that speed induction also speed recovery: elimination of rebreathing, high fresh gas flows, low anesthetic-circuit volume, low absorption by the anesthetic circuit, decreased solubility, high cerebral blood flow (CBF), and increased ventilation. Elimination of nitrous oxide is so rapid that alveolar oxygen and CO_2 are diluted. The resulting **diffusion hypoxia** is prevented by administering 100% oxygen for 5–10 min after discontinuing nitrous oxide. The rate of recovery is usually faster than induction because tissues that have not reached equilibrium will continue to take up anesthetic until the alveolar partial pressure falls below the tissue partial pressure. For instance, fat will continue to take up anesthetic and hasten recovery until the partial pressure exceeds the alveolar partial pressure. This redistribution is not as useful after prolonged anesthesia (fat partial pressures of anesthetic will have come "closer" to arterial partial pressures at the time the anesthetic was removed from fresh gas)—thus, the speed of recovery also depends on the length of time the anesthetic has been administered.

Pharmacodynamics of Inhalation Anesthetics

THEORIES OF ANESTHETIC ACTION

General anesthesia is an altered physiological state characterized by reversible loss of consciousness, analgesia, amnesia, and some degree of muscle relaxation. The multitude of substances capable of producing general anesthesia is remarkable: inert elements (xenon), simple inorganic compounds (nitrous oxide), halogenated hydrocarbons (halothane), ethers (isoflurane, sevoflurane, desflurane), and complex organic structures (propofol). A unifying theory explaining anesthetic action would have to accommodate this diversity of structure. In fact, the various agents probably produce anesthesia by differing sets of molecular mechanisms. Inhalational agents interact with numerous ion channels present in the CNS and peripheral nervous system. Nitrous oxide and xenon are believed to inhibit *N*-methyl-D-aspartate (NMDA) receptors. NMDA receptors are excitatory receptors in the brain. Other inhalational agents may interact at other receptors

(eg, gamma-aminobutyric acid [GABA]-activated chloride channel conductance) leading to anesthetic effects. Additionally, some studies suggest that inhalational agents continue to act in a nonspecific manner, thereby affecting the membrane bilayer. It is possible that inhalational anesthetics act on multiple protein receptors that block excitatory channels and promote the activity of inhibitory channels affecting neuronal activity, as well as by some nonspecific membrane effects.

There does not seem to be a single macroscopic site of action that is shared by all inhalation agents. Specific brain areas affected by various anesthetics include the reticular activating system, the cerebral cortex, the cuneate nucleus, the olfactory cortex, and the hippocampus; however, to be clear, general anesthetics bind throughout the CNS. Anesthetics have also been shown to depress excitatory transmission in the spinal cord, particularly at the level of the dorsal horn interneurons that are involved in pain transmission. Differing aspects of anesthesia may be related to different sites of anesthetic action. For example, unconsciousness and amnesia are probably mediated by cortical anesthetic action, whereas the suppression of purposeful withdrawal from pain may be related to subcortical structures, such as the spinal cord or brain stem. One study in rats revealed that removal of the cerebral cortex did not alter the potency of the anesthetic! Indeed, measures of minimal alveolar concentration (MAC), the anesthetic concentration that prevents movement in 50% of subjects or animals, are dependent upon anesthetic effects at the spinal cord and not at the cortex.

5 Past understanding of anesthetic action attempted to identify a unitary hypothesis of anesthetic effects. This hypothesis proposes that all inhalation agents share a common mechanism of action at the molecular level. This was previously supported by the observation that the anesthetic potency of inhalation agents correlates directly with their lipid solubility (Meyer–Overton rule). The implication is that anesthesia results from molecules dissolving at specific lipophilic sites. Of course, not all lipid-soluble molecules are anesthetics (some are actually convulsants), and the correlation between anesthetic potency and lipid solubility is only approximate (**Figure 8–4**).

Neuronal membranes contain a multitude of hydrophobic sites in their phospholipid bilayer. Anesthetic binding to these sites could expand the bilayer beyond a critical amount, altering membrane function (critical volume hypothesis). Although this theory is almost certainly an oversimplification, it explains an interesting phenomenon: the reversal of anesthesia by increased pressure. Laboratory animals exposed to elevated hydrostatic pressure develop a resistance to anesthetic effects. Perhaps the pressure is displacing a number of molecules from the membrane or distorting the anesthetic binding sites in the membrane, increasing anesthetic requirements. However, studies in the 1980s demonstrated the ability of anesthetics to inhibit protein actions, shifting attention to the numerous ion channels that might affect neuronal transmission and away from the critical volume hypothesis.

General anesthetic action could be due to alterations in any one (or a combination) of several cellular systems, including voltage-gated ion channels, ligand-gated ion channels, second messenger functions, or neurotransmitter receptors. For example, many anesthetics enhance GABA inhibition of the CNS. Furthermore, GABA receptor agonists seem to enhance anesthesia, whereas GABA antagonists reverse some anesthetic effects. There seems to be a strong correlation between anesthetic potency and potentiation of GABA receptor activity. Thus, anesthetic action may relate to binding in relatively hydrophobic domains in channel proteins (GABA receptors). Modulation of GABA function may prove to be a principal mechanism of action for many anesthetic drugs.

The glycine receptor α_1-subunit, whose function is enhanced by inhalation anesthetics, is another potential anesthetic site of action.

The tertiary and quaternary structure of amino acids within an anesthetic-binding pocket could be modified by inhalation agents, perturbing the receptor itself, or indirectly producing an effect at a distant site.

Other ligand-gated ion channels whose modulation may play a role in anesthetic action include nicotinic acetylcholine receptors and NMDA receptors.

Investigations into mechanisms of anesthetic action are likely to remain ongoing for many years,

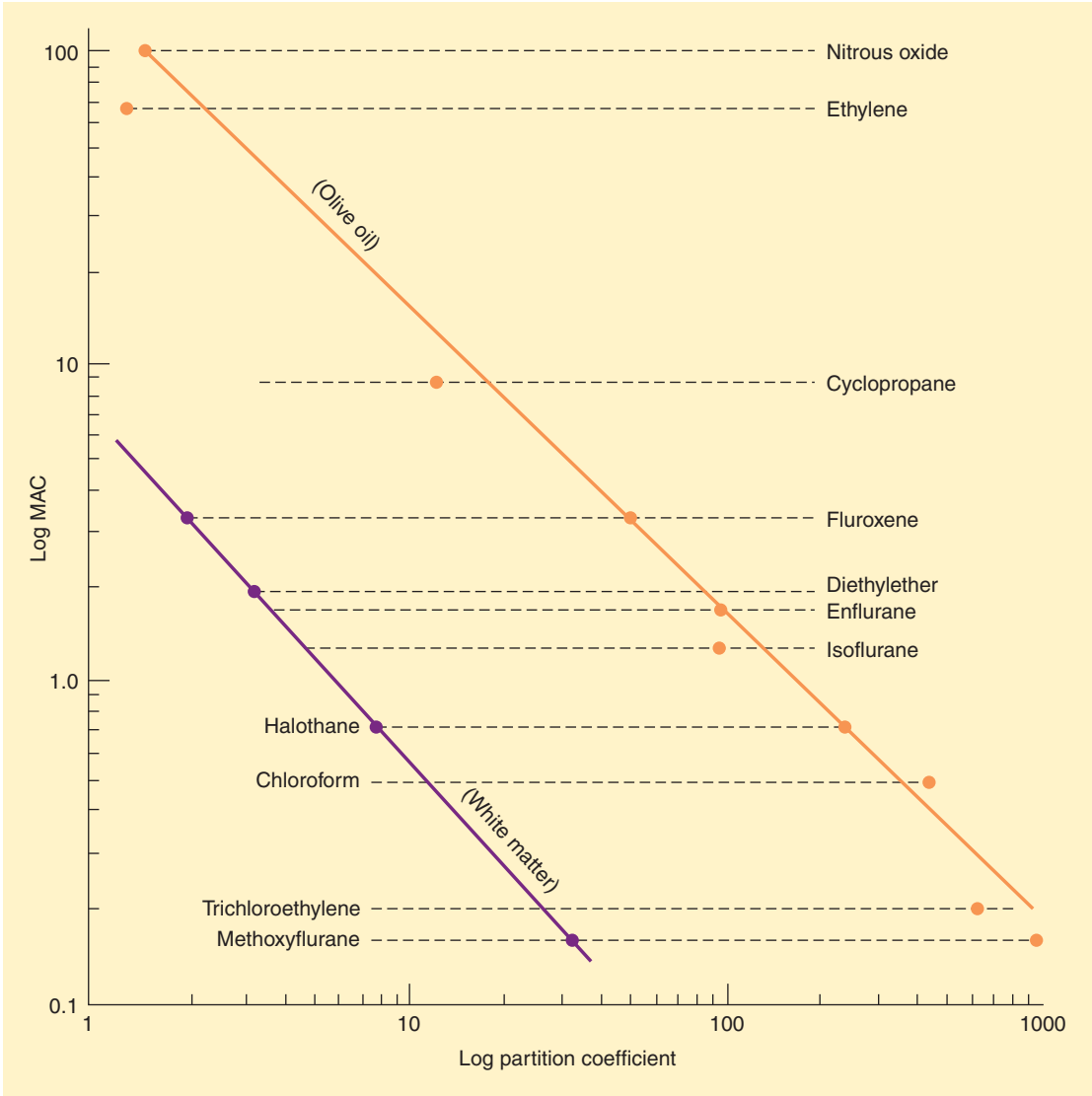


FIGURE 8–4 There is a good but not perfect correlation between anesthetic potency and lipid solubility. MAC, minimum alveolar concentration. (Modified and reproduced, with permission, from Lowe HJ, Hagler K: *Gas Chromatography in Biology and Medicine*. Churchill, 1969.)

as many protein channels may be affected by individual anesthetic agents, and no obligatory site has yet been identified. Selecting among so many molecular targets for the one(s) that provide optimum effects with minimal adverse actions will be the challenge in designing better inhalational agents.

ANESTHETIC NEUROTOXICITY

In recent years, there has been ongoing concern that general anesthetics damage the developing brain. It has been suggested that early exposure to anesthetics can promote cognitive impairment in later life. Concern has been raised that anesthetic exposure

affects the development and the elimination of synapses in the infant brain. For example, animal studies have demonstrated that isoflurane exposure promotes neuronal apoptosis and subsequent learning disability. Volatile anesthetics have been shown to promote apoptosis by altering cellular calcium homeostatic mechanisms.

Human studies exploring whether anesthesia is harmful in children are difficult, as conducting a randomized controlled trial for that purpose only would be unethical. Studies that compare populations of children who have had anesthetics with those who have not are also complicated by the reality that the former population is likewise having surgery and receiving the attention of the medical community. Consequently, children receiving anesthetics may be more likely to be diagnosed with learning difficulties in the first place. Data from one large study demonstrated that children who underwent surgery and anesthesia had a greater likelihood of carrying the diagnosis of a developmental disorder; however, the finding was not supported in twins (ie, the incidence of developmental disability was not greater in a twin who was exposed to anesthesia and surgery than in one who was not).

Human, animal, and laboratory trials demonstrating or refuting that anesthetic neurotoxicity leads to developmental disability in children are underway. As of this writing, there is insufficient and conflicting evidence to warrant changes in anesthetic practice (see: www.smarttots.org).

ANESTHETIC NEUROPROTECTION AND CARDIAC PRECONDITIONING

Although inhalational agents have been suggested as contributing to neurotoxicity, they have also been shown to provide both neurologic and cardiac protective effects against ischemia-reperfusion injury. Ischemic preconditioning implies that a brief ischemic episode protects a cell from future, more pronounced ischemic events. Various molecular mechanisms have been suggested to protect cells preconditioned either through ischemic events or secondary to pharmacologic mechanisms, such as through the use of inhalational anesthetics. In the heart, preconditioning in part arises from actions at ATP-sensitive potassium (K_{ATP}) channels.

The exact mechanism of anesthetic preconditioning is likely to be multifocal and includes the opening of K_{ATP} channels, resulting in less mitochondrial calcium ion concentration and reduction of reactive oxygen species (ROS) production. ROS are associated with cellular injury. For example, excitatory NMDA receptors are linked to the development of neuronal injury. NMDA antagonists, such as the noble anesthetic gas Xenon, have been shown to be neuroprotective. Xenon has an anti-apoptotic effect that may be secondary to its inhibition of calcium ion influx following cell injury. Other inhalational agents, such as sevoflurane, have been shown to reduce markers of myocardial cell injury (eg, troponin T), compared with intravenous anesthetic techniques.

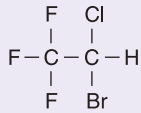
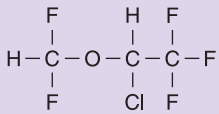
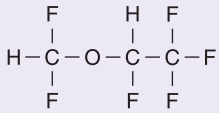
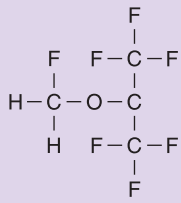
As with neurotoxicity, the role of inhalational anesthetics in tissue protection is the subject of ongoing investigation.

MINIMUM ALVEOLAR CONCENTRATION

6 The minimum alveolar concentration (MAC) of an inhaled anesthetic is the alveolar concentration that prevents movement in 50% of patients in response to a standardized stimulus (eg, surgical incision). MAC is a useful measure because it mirrors brain partial pressure, allows comparisons of potency between agents, and provides a standard for experimental evaluations (Table 8–3). Nonetheless, it should be remembered that this is a median value with limited usefulness in managing individual patients, particularly during times of rapidly changing alveolar concentrations (eg, induction).

The MAC values for different anesthetics are roughly additive. For example, a mixture of 0.5 MAC of nitrous oxide (53%) and 0.5 MAC of halothane (0.37%) produces the same likelihood that movement in response to surgical incision will be suppressed as 1.0 MAC of isoflurane (1.7%) or 1.0 MAC of any other single agent. In contrast to CNS depression, the degree of myocardial depression may not be equivalent at the same MAC: 0.5 MAC of halothane causes more myocardial depression than 0.5 MAC

TABLE 8–3 Properties of modern inhalation anesthetics.

Agent	Structure	MAC%[1]	Vapor Pressure (mm Hg at 20°C)
Nitrous oxide		105[2]	—
Halothane (Fluothane)		0.75	243
Isoflurane (Forane)		1.2	240
Desflurane (Suprane)		6.0	681
Sevoflurane (Ultane)		2.0	160

[1]These minimum alveolar concentration (MAC) values are for 30- to 55-year old human subjects and are expressed as a percentage of 1 atmosphere. High altitude requires a higher inspired concentration of anesthetic to achieve the same partial pressure.

[2]A concentration greater than 100% means that hyperbaric conditions are required to achieve 1.0 MAC.

of nitrous oxide. MAC represents only one point on the dose–response curve—it is the equivalent of a median effective dose (ED_{50}). MAC multiples are clinically useful if the concentration–response curves of the anesthetics being compared are parallel, nearly linear, and continuous for the effect being predicted. Roughly 1.3 MAC of any of the volatile anesthetics (eg, for halothane: $1.3 \times 0.74\% = 0.96\%$) has been found to prevent movement in about 95% of patients (an approximation of the ED_{95}); 0.3–0.4 MAC is associated with awakening from anesthesia (MAC awake) when the inhaled drug is the only agent maintaining anesthetic (a rare circumstance).

MAC can be altered by several physiological and pharmacological variables (Table 8–4). **One of the most striking is the 6% decrease in MAC per decade of age, regardless of volatile anesthetic**. MAC is relatively unaffected by species, sex, or duration of anesthesia. Surprisingly, MAC is not altered after spinal cord transection in rats, leading to the hypothesis that the site of anesthetic inhibition of motor responses lies in the spinal cord.

Clinical Pharmacology of Inhalation Anesthetics

NITROUS OXIDE

Physical Properties

Nitrous oxide (N_2O; laughing gas) is colorless and essentially odorless. Although nonexplosive and nonflammable, nitrous oxide is as capable as oxygen of supporting combustion. Unlike the potent volatile

TABLE 8–4 Factors affecting MAC.[1]

Variable	Effect on MAC	Comments	Variable	Effect on MAC	Comments
Temperature			Electrolytes		
Hypothermia	↓		Hypercalcemia	↓	
Hyperthermia	↓	↑ if > 42°C	Hypernatremia	↑	Caused by altered CSF[2]
			Hyponatremia	↓	Caused by altered CSF
Age			Pregnancy	↓	MAC decreased by one-third at 8 weeks' gestation; normal by 72 h postpartum
Young	↑				
Elderly	↓				
Alcohol			Drugs		
Acute intoxication	↓		Local anesthetics	↓	Except cocaine
Chronic abuse	↑		Opioids	↓	
			Ketamine	↓	
Anemia			Barbiturates	↓	
Hematocrit < 10%	↓		Benzodiazepines	↓	
			Verapamil	↓	
PaO_2	↓		Lithium	↓	
<40 mm Hg			Sympatholytics		
			Methyldopa	↓	
$Paco_2$			Clonidine	↓	
>95 mm Hg	↓	Caused by < pH in CSF	Dexmedetomidine	↓	
			Sympathomimetics		
Thyroid			Amphetamine		
Hyperthyroid	No change		Chronic	↓	
Hypothyroid	No change		Acute	↑	
			Cocaine	↑	
Blood pressure			Ephedrine	↑	
Mean arterial pressure <40 mm Hg	↓				

[1]These conclusions are based on human and animal studies.
[2]CSF, cerebrospinal fluid.

agents, nitrous oxide is a gas at room temperature and ambient pressure. It can be kept as a liquid under pressure because its critical temperature lies above room temperature. Nitrous oxide is a relatively inexpensive anesthetic; however, concerns regarding its safety have led to continued interest in alternatives such as **xenon** (Table 8–5). As noted earlier, nitrous oxide, like xenon, is an NMDA receptor antagonist.

TABLE 8–5 Advantages and disadvantages of xenon (Xe) anesthesia.

Advantages
Inert (probably nontoxic with no metabolism)
Minimal cardiovascular effects
Low blood solubility
Rapid induction and recovery
Does not trigger malignant hyperthermia
Environmentally friendly
Nonexplosive
Disadvantages
High cost
Low potency (MAC = 70%)[1]

[1]MAC, minimum alveolar concentration.

Effects on Organ Systems

A. Cardiovascular

Nitrous oxide has a tendency to stimulate the sympathetic nervous system. Thus, even though nitrous oxide directly depresses myocardial contractility in

TABLE 8–6 Clinical pharmacology of inhalational anesthetics.

	Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular					
Blood pressure	N/C[1]	↓↓	↓↓	↓↓	↓
Heart rate	N/C	↓	↑	N/C or ↑	N/C
Systemic vascular resistance	N/C	N/C	↓↓	↓↓	↓
Cardiac output[2]	N/C	↓	N/C	N/C or ↓	↓
Respiratory					
Tidal volume	↓	↓↓	↓↓	↓	↓
Respiratory rate	↑	↑↑	↑	↑	↑
$Paco_2$					
Resting	N/C	↑	↑	↑↑	↑
Challenge	↑	↑	↑	↑↑	↑
Cerebral					
Blood flow	↑	↑↑	↑	↑	↑
Intracranial pressure	↑	↑↑	↑	↑	↑
Cerebral metabolic rate	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Neuromuscular					
Nondepolarizing blockade[3]	↑	↑↑	↑↑↑	↑↑↑	↑↑
Renal					
Renal blood flow	↓↓	↓↓	↓↓	↓	↓
Glomerular filtration rate	↓↓	↓↓	↓↓	↓	↓
Urinary output	↓↓	↓↓	↓↓	↓	↓
Hepatic					
Blood flow	↓	↓↓	↓	↓	↓
Metabolism[4]	0.004%	15% to 20%	0.2%	<0.1%	5%

[1]N/C, no change.
[2]Controlled ventilation.
[3]Depolarizing blockage is probably also prolonged by these agents, but this is usually not clinically significant.
[4]Percentage of absorbed anesthetic undergoing metabolism.

vitro, arterial blood pressure, cardiac output, and heart rate are essentially unchanged or slightly elevated in vivo because of its stimulation of catecholamines (Table 8–6). Myocardial depression may be unmasked in patients with coronary artery disease or severe hypovolemia. Constriction of pulmonary vascular smooth muscle increases pulmonary vascular resistance, which results in a generally modest elevation of right ventricular end-diastolic pressure. Despite vasoconstriction of cutaneous vessels, peripheral vascular resistance is not significantly altered.

B. Respiratory

Nitrous oxide increases respiratory rate (tachypnea) and decreases tidal volume as a result of CNS stimulation and, perhaps, activation of pulmonary stretch receptors. The net effect is a minimal change in minute ventilation and resting arterial CO_2 levels. Hypoxic drive, the ventilatory response to arterial hypoxia that is mediated by peripheral chemoreceptors in the carotid bodies, is markedly depressed by even small amounts of nitrous oxide. This is a concern in the recovery room.

C. Cerebral

By increasing CBF and cerebral blood volume, nitrous oxide produces a mild elevation of intracranial pressure. Nitrous oxide also increases cerebral oxygen consumption ($CMRO_2$). These two effects make nitrous oxide theoretically less attractive than

other agents for neuroanesthesia. Concentrations of nitrous oxide below MAC may provide analgesia in dental surgery, labor, traumatic injury, and minor surgical procedures.

D. Neuromuscular

In contrast to other inhalation agents, nitrous oxide does not provide significant muscle relaxation. In fact, at high concentrations in hyperbaric chambers, nitrous oxide causes skeletal muscle rigidity. Nitrous oxide is not a triggering agent of malignant hyperthermia.

E. Renal

Nitrous oxide seems to decrease renal blood flow by increasing renal vascular resistance. This leads to a drop in glomerular filtration rate and urinary output.

F. Hepatic

Hepatic blood flow probably falls during nitrous oxide anesthesia, but to a lesser extent than with the volatile agents.

G. Gastrointestinal

Use of nitrous oxide in adults increases the risk of postoperative nausea and vomiting, presumably as a result of activation of the chemoreceptor trigger zone and the vomiting center in the medulla.

Biotransformation & Toxicity

During emergence, almost all nitrous oxide is eliminated by exhalation. A small amount diffuses out through the skin. Biotransformation is limited to the less than 0.01% that undergoes reductive metabolism in the gastrointestinal tract by anaerobic bacteria.

By irreversibly oxidizing the cobalt atom in vitamin B_{12}, nitrous oxide inhibits enzymes that are vitamin B_{12} dependent. These enzymes include methionine synthetase, which is necessary for myelin formation, and thymidylate synthetase, which is necessary for DNA synthesis. Prolonged exposure to anesthetic concentrations of nitrous oxide can result in bone marrow depression (megaloblastic anemia) and even neurological deficiencies (peripheral neuropathies). However, administration of nitrous oxide for bone marrow harvest does not seem to affect the viability of bone marrow mononuclear cells. Because of possible teratogenic effects, nitrous oxide is often avoided in pregnant patients who are not yet in the third trimester. Nitrous oxide may also alter the immunological response to infection by affecting chemotaxis and motility of polymorphonuclear leukocytes.

Contraindications

Although nitrous oxide is insoluble in comparison with other inhalation agents, it is 35 times more soluble than nitrogen in blood. Thus, it tends to diffuse into air-containing cavities more rapidly than nitrogen is absorbed by the bloodstream. For instance, if a patient with a 100-mL pneumothorax inhales 50% nitrous oxide, the gas content of the pneumothorax will tend to approach that of the bloodstream. Because nitrous oxide will diffuse into the cavity more rapidly than the air (principally nitrogen) diffuses out, the pneumothorax expands until it contains 100 mL of air and 100 mL of nitrous oxide. If the walls surrounding the cavity are rigid, pressure rises instead of volume. **Examples of conditions in which nitrous oxide might be hazardous include venous or arterial air embolism, pneumothorax, acute intestinal obstruction with bowel distention, intracranial air (pneumocephalus following dural closure or pneumoencephalography), pulmonary air cysts, intraocular air bubbles, and tympanic membrane grafting**. Nitrous oxide will even diffuse into tracheal tube cuffs, increasing the pressure against the tracheal mucosa. Obviously, nitrous oxide is of limited value in patients requiring high inspired oxygen concentrations.

Drug Interactions

Because the high MAC of nitrous oxide prevents its use as a complete general anesthetic, it is frequently used in combination with the more potent volatile agents. The addition of nitrous oxide decreases the requirements of these other agents (65% nitrous oxide decreases the MAC of the volatile anesthetics by approximately 50%). Although nitrous oxide should not be considered a benign carrier gas, it does attenuate the circulatory and respiratory effects of volatile anesthetics in adults. Nitrous oxide

potentiates neuromuscular blockade, but less so than the volatile agents. The concentration of nitrous oxide flowing through a vaporizer can influence the concentration of volatile anesthetic delivered. For example, decreasing nitrous oxide concentration (ie, increasing oxygen concentration) increases the concentration of volatile agent despite a constant vaporizer setting. This disparity is due to the relative solubilities of nitrous oxide and oxygen in liquid volatile anesthetics. The second gas effect was discussed earlier. Nitrous oxide is an ozone-depleting gas with greenhouse effects.

HALOTHANE

Physical Properties

Halothane is a halogenated alkane (see Table 8–3). The carbon–fluoride bonds are responsible for its nonflammable and nonexplosive nature. Thymol preservative and amber-colored bottles retard spontaneous oxidative decomposition. It is rarely used in the United States.

Effects on Organ Systems

A. Cardiovascular

A dose-dependent reduction of arterial blood pressure is due to direct myocardial depression; 2.0 MAC of halothane in patients not undergoing surgery results in a 50% decrease in blood pressure and cardiac output. Cardiac depression—from interference with sodium–calcium exchange and intracellular calcium utilization—causes an increase in right atrial pressure. Although halothane is a coronary artery vasodilator, coronary blood flow decreases, due to the drop in systemic arterial pressure. Adequate myocardial perfusion is usually maintained, as oxygen demand also drops. Normally, hypotension inhibits baroreceptors in the aortic arch and carotid bifurcation, causing a decrease in vagal stimulation and a compensatory rise in heart rate. Halothane blunts this reflex. Slowing of sinoatrial node conduction may result in a junctional rhythm or bradycardia. In infants, halothane decreases cardiac output by a combination of decreased heart rate and depressed myocardial contractility. Halothane sensitizes the heart to the arrhythmogenic effects of epinephrine, so that doses of epinephrine above 1.5 mcg/kg should be avoided. Although organ blood flow is redistributed, systemic vascular resistance is unchanged.

B. Respiratory

Halothane typically causes rapid, shallow breathing. The increased respiratory rate is not enough to counter the decreased tidal volume, so alveolar ventilation drops, and resting $Paco_2$ is elevated. **Apneic threshold**, the highest $Paco_2$ at which a patient remains apneic, also rises because the difference between it and resting $Paco_2$ is not altered by general anesthesia. Similarly, halothane limits the increase in minute ventilation that normally accompanies a rise in $Paco_2$. Halothane's ventilatory effects are probably due to central (medullary depression) and peripheral (intercostal muscle dysfunction) mechanisms. These changes are exaggerated by preexisting lung disease and attenuated by surgical stimulation. The increase in $Paco_2$ and the decrease in intrathoracic pressure that accompany spontaneous ventilation with halothane partially reverse the depression in cardiac output, arterial blood pressure, and heart rate described above. Hypoxic drive is severely depressed by even low concentrations of halothane (0.1 MAC).

Halothane is considered a potent bronchodilator, as it often reverses asthma-induced bronchospasm. This action is not inhibited by β-adrenergic blocking agents. Halothane attenuates airway reflexes and relaxes bronchial smooth muscle by inhibiting intracellular calcium mobilization. Halothane also depresses clearance of mucus from the respiratory tract (mucociliary function), promoting postoperative hypoxia and atelectasis.

C. Cerebral

By dilating cerebral vessels, halothane lowers cerebral vascular resistance and increases CBF. **Autoregulation**, the maintenance of constant CBF during changes in arterial blood pressure, is blunted. Concomitant rises in intracranial pressure can be prevented by establishing hyperventilation *prior to* administration of halothane. Cerebral activity is decreased, leading to electroencephalographic slowing and modest reductions in metabolic oxygen requirements.

D. Neuromuscular

Halothane relaxes skeletal muscle and potentiates nondepolarizing neuromuscular-blocking agents (NMBA). Like the other potent volatile anesthetics, it is a triggering agent of malignant hyperthermia.

E. Renal

Halothane reduces renal blood flow, glomerular filtration rate, and urinary output. Part of this decrease can be explained by a fall in arterial blood pressure and cardiac output. Because the reduction in renal blood flow is greater than the reduction in glomerular filtration rate, the filtration fraction is increased. Preoperative hydration limits these changes.

F. Hepatic

Halothane causes hepatic blood flow to decrease in proportion to the depression of cardiac output. Hepatic artery vasospasm has been reported during halothane anesthesia. The metabolism and clearance of some drugs (eg, fentanyl, phenytoin, verapamil) seem to be impaired by halothane. Other evidence of hepatic cellular dysfunction includes sulfobromophthalein (BSP) dye retention and minor liver transaminase elevations.

Biotransformation & Toxicity

Halothane is oxidized in the liver by a particular isozyme of CYP (2EI) to its principal metabolite, trifluoroacetic acid. This metabolism can be inhibited by pretreatment with disulfiram. Bromide, another oxidative metabolite, has been incriminated in (but is an improbable cause of) postanesthetic changes in mental status. In the absence of oxygen, reductive metabolism may result in a small amount of hepatotoxic end products that covalently bind to tissue macromolecules. This is more apt to occur following enzyme induction by phenobarbital. Elevated fluoride levels signal significant anaerobic metabolism.

Postoperative hepatic dysfunction has several causes: viral hepatitis, impaired hepatic perfusion, preexisting liver disease, hepatocyte hypoxia, sepsis, hemolysis, benign postoperative intrahepatic cholestasis, and drug-induced hepatitis. "**Halothane hepatitis"** is extremely rare (1 per 35,000 cases). Patients exposed to multiple halothane anesthetics at short intervals, middle-aged obese women, and persons with a familial predisposition to halothane toxicity or a personal history of toxicity are considered to be at increased risk. Signs are mostly related to hepatic injury, such as increased serum alanine and aspartate transferase, elevated bilirubin (leading to jaundice), and encephalopathy.

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The hepatic lesion seen in humans—centrilobular necrosis—also occurs in rats pretreated with an enzyme inducer (phenobarbital) and exposed to halothane under hypoxic conditions ($F_{IO_2} < 14\%$). This *halothane hypoxic model* implies hepatic damage from reductive metabolites or hypoxia.

More likely evidence points to an immune mechanism. For instance, some signs of the disease indicate an allergic reaction (eg, eosinophilia, rash, fever) and do not appear until a few days after exposure. Furthermore, an antibody that binds to hepatocytes previously exposed to halothane has been isolated from patients with halothane-induced hepatic dysfunction. This antibody response may involve liver microsomal proteins that have been modified by trifluoroacetic acid as the triggering antigens (trifluoroacetylated liver proteins such as microsomal carboxylesterase). As with halothane, other inhalational agents that undergo oxidative metabolism can likewise lead to hepatitis. However, newer agents undergo little to no metabolism, and therefore do not form trifluroacetic acid protein adducts or produce the immune response leading to hepatitis.

Contraindications

It is prudent to withhold halothane from patients with unexplained liver dysfunction following previous anesthetic exposure.

Halothane, like all inhalational anesthetics, should be used with care in patients with intracranial mass lesions because of the possibility of intracranial hypertension secondary to increased cerebral blood volume and blood flow.

Hypovolemic patients and some patients with severe reductions in left ventricular function may not tolerate halothane's negative inotropic effects. Sensitization of the heart to catecholamines limits the usefulness of halothane when exogenous epinephrine is administered or in patients with pheochromocytoma.

Drug Interactions

The myocardial depression seen with halothane is exacerbated by β-adrenergic-blocking agents and calcium channel-blocking agents. Tricyclic antidepressants and monoamine oxidase inhibitors have been associated with fluctuations in blood pressure and arrhythmias, although neither represents an absolute contraindication. The combination of halothane and aminophylline has resulted in serious ventricular arrhythmias.

ISOFLURANE

Physical Properties

Isoflurane is a nonflammable volatile anesthetic with a pungent ethereal odor. Although it is a chemical isomer with the same molecular weight as enflurane, it has different physicochemical properties (see Table 8–3).

Effects on Organ Systems

A. Cardiovascular

Isoflurane causes minimal left ventricular depression in vivo. Cardiac output is maintained by a rise in heart rate due to partial preservation of carotid baroreflexes. Mild β-adrenergic stimulation increases skeletal muscle blood flow, decreases systemic vascular resistance, and lowers arterial blood pressure. Rapid increases in isoflurane concentration lead to transient increases in heart rate, arterial blood pressure, and plasma levels of norepinephrine. Isoflurane dilates coronary arteries, but not nearly as potently as nitroglycerin or adenosine. Dilation of normal coronary arteries could theoretically divert blood away from fixed stenotic lesions, which was the basis for concern about coronary "steal" with this agent, a concern that has largely been forgotten.

B. Respiratory

Respiratory depression during isoflurane anesthesia resembles that of other volatile anesthetics, except that tachypnea is less pronounced. The net effect is a more pronounced fall in minute ventilation. Even low levels of isoflurane (0.1 MAC) blunt the normal ventilatory response to hypoxia and hypercapnia. Despite a tendency to irritate upper airway reflexes, isoflurane is considered a good bronchodilator, but may not be as potent a bronchodilator as halothane.

C. Cerebral

At concentrations greater than 1 MAC, isoflurane increases CBF and intracranial pressure. These effects are thought to be less pronounced than with halothane and are reversed by hyperventilation. In contrast to halothane, the hyperventilation does not have to be instituted prior to the use of isoflurane to prevent intracranial hypertension. Isoflurane reduces cerebral metabolic oxygen requirements, and at 2 MAC, it produces an electrically silent electroencephalogram (EEG).

D. Neuromuscular

Isoflurane relaxes skeletal muscle.

E. Renal

Isoflurane decreases renal blood flow, glomerular filtration rate, and urinary output.

F. Hepatic

Total hepatic blood flow (hepatic artery and portal vein flow) may be reduced during isoflurane anesthesia. Hepatic oxygen supply is better maintained with isoflurane than with halothane, however, because hepatic artery perfusion is preserved. Liver function tests are usually not affected.

Biotransformation & Toxicity

Isoflurane is metabolized to trifluoroacetic acid. Although serum fluoride fluid levels may rise, nephrotoxicity is extremely unlikely, even in the presence of enzyme inducers. Prolonged sedation (>24 h at 0.1–0.6% isoflurane) of critically ill patients has resulted in elevated plasma fluoride levels (15–50 μmol/L) without evidence of renal impairment. Similarly, up to 20 MAC-hours of isoflurane may lead to fluoride levels exceeding 50 μmol/L without detectable postoperative renal dysfunction. Its limited oxidative metabolism also minimizes any possible risk of significant hepatic dysfunction.

Contraindications

Isoflurane presents no unique contraindications. Patients with severe hypovolemia may not tolerate

its vasodilating effects. It can trigger malignant hyperthermia.

Drug Interactions

Epinephrine can be safely administered in doses up to 4.5 mcg/kg. Nondepolarizing NMBAs are potentiated by isoflurane.

DESFLURANE

Physical Properties

The structure of desflurane is very similar to that of isoflurane. In fact, the only difference is the substitution of a fluorine atom for isoflurane's chlorine atom. That "minor" change has profound effects on the physical properties of the drug, however. For instance, because the vapor pressure of desflurane at 20°C is 681 mm Hg, at high altitudes (eg, Denver, Colorado) it boils at room temperature. This problem necessitated the development of a special desflurane vaporizer. Furthermore, the low solubility of desflurane in blood and body tissues causes a very rapid induction and emergence of anesthesia. Therefore, the alveolar concentration of desflurane approaches the inspired concentration much more rapidly than the other volatile agents, giving the anesthesiologist tighter control over anesthetic levels. **Wakeup times are approximately 50% less than those observed following isoflurane**. This is principally attributable to a blood/gas partition coefficient (0.42) that is even lower than that of nitrous oxide (0.47). Although desflurane is roughly one-fourth as potent as the other volatile agents, it is 17 times more potent than nitrous oxide. A high vapor pressure, an ultrashort duration of action, and moderate potency are the most characteristic features of desflurane.

Effects on Organ Systems

A. Cardiovascular

The cardiovascular effects of desflurane seem to be similar to those of isoflurane. Increasing the dose is associated with a decline in systemic vascular resistance that leads to a fall in arterial blood pressure. Cardiac output remains relatively unchanged or slightly depressed at 1–2 MAC. There is a moderate rise in heart rate, central venous pressure, and pulmonary artery pressure that often does not become apparent at low doses. Rapid increases in desflurane concentration lead to transient but sometimes worrisome elevations in heart rate, blood pressure, and catecholamine levels that are more pronounced than occur with isoflurane, particularly in patients with cardiovascular disease. These cardiovascular responses to rapidly increasing desflurane concentration can be attenuated by fentanyl, esmolol, or clonidine.

B. Respiratory

Desflurane causes a decrease in tidal volume and an increase in respiratory rate. There is an overall decrease in alveolar ventilation that causes a rise in resting $Paco_2$. Like other modern volatile anesthetic agents, desflurane depresses the ventilatory response to increasing $Paco_2$. Pungency and airway irritation during desflurane induction can be manifested by salivation, breath-holding, coughing, and laryngospasm. Airway resistance may increase in children with reactive airway susceptibility. These problems make desflurane a poor choice for inhalation induction.

C. Cerebral

Like the other volatile anesthetics, desflurane directly vasodilates the cerebral vasculature, increasing CBF, cerebral blood volume, and intracranial pressure at normotension and normocapnia. Countering the decrease in cerebral vascular resistance is a marked decline in the cerebral metabolic rate of oxygen ($CMRO_2$) that tends to cause cerebral vasoconstriction and moderate any increase in CBF. The cerebral vasculature remains responsive to changes in $Paco_2$, however, so that intracranial pressure can be lowered by hyperventilation. Cerebral oxygen consumption is decreased during desflurane anesthesia. Thus, during periods of desflurane-induced hypotension (mean arterial pressure = 60 mm Hg), CBF is adequate to maintain aerobic metabolism despite a low cerebral perfusion pressure. The effect on the EEG is similar to that of isoflurane. Initially, EEG frequency is increased, but as anesthetic depth is increased, EEG slowing

becomes manifest, leading to burst suppression at higher inhaled concentrations.

D. Neuromuscular

Desflurane is associated with a dose-dependent decrease in the response to train-of-four and tetanic peripheral nerve stimulation.

E. Renal

There is no evidence of any significant nephrotoxic effects caused by exposure to desflurane. However, as cardiac output declines, decreases in urine output and glomerular filtration should be expected with desflurane and all other anesthetics.

F. Hepatic

Hepatic function tests are generally unaffected by desflurane, assuming that organ perfusion is maintained perioperatively. Desflurane undergoes minimal metabolism, therefore the risk of anesthetic-induced hepatitis is likewise minimal. As with isoflurane and sevoflurane, hepatic oxygen delivery is generally maintained.

Biotransformation & Toxicity

Desflurane undergoes minimal metabolism in humans. Serum and urine inorganic fluoride levels following desflurane anesthesia are essentially unchanged from preanesthetic levels. There is insignificant percutaneous loss. Desflurane, more than other volatile anesthetics, is degraded by desiccated CO_2 absorbent (particularly barium hydroxide lime, but also sodium and potassium hydroxide) into potentially clinically significant levels of carbon monoxide. Carbon monoxide poisoning is difficult to diagnose under general anesthesia, but the presence of carboxyhemoglobin may be detectable by arterial blood gas analysis or lower than expected pulse oximetry readings (although still falsely high). Disposing of dried out absorbent or use of calcium hydroxide can minimize the risk of carbon monoxide poisoning.

Contraindications

Desflurane shares many of the contraindications of other modern volatile anesthetics: severe hypovolemia, malignant hyperthermia, and intracranial hypertension.

Drug Interactions

Desflurane potentiates nondepolarizing neuromuscular blocking agents to the same extent as isoflurane. Epinephrine can be safely administered in doses up to 4.5 mcg/kg as desflurane does not sensitize the myocardium to the arrhythmogenic effects of epinephrine. Although emergence is more rapid following desflurane anesthesia than after isoflurane anesthesia, switching from isoflurane to desflurane toward the end of anesthesia does not significantly accelerate recovery, nor does faster emergence translate into faster discharge times from the post-anesthesia care unit. Desflurane emergence has been associated with delirium in some pediatric patients.

SEVOFLURANE

Physical Properties

Like desflurane, sevoflurane is halogenated with fluorine. Sevoflurane's solubility in blood is slightly greater than desflurane ($\lambda_{b/g}$ 0.65 versus 0.42) 12 (see Table 8–3). Nonpungency and rapid increases in alveolar anesthetic concentration make sevoflurane an excellent choice for smooth and rapid inhalation inductions in pediatric and adult patients. In fact, inhalation induction with 4% to 8% sevoflurane in a 50% mixture of nitrous oxide and oxygen can be achieved within 1 min. Likewise, its low blood solubility results in a rapid fall in alveolar anesthetic concentration upon discontinuation and a more rapid emergence compared with isoflurane (although not an earlier discharge from the post-anesthesia care unit). Sevoflurane's modest vapor pressure permits the use of a conventional variable bypass vaporizer.

Effects on Organ Systems

A. Cardiovascular

Sevoflurane mildly depresses myocardial contractility. Systemic vascular resistance and arterial blood pressure decline slightly less than with isoflurane or desflurane. Because sevoflurane causes little, if any, rise in heart rate, cardiac output is not maintained as well as with isoflurane or desflurane. Sevoflurane

may prolong the QT interval, the clinical significance of which is unknown. QT prolongation may be manifest 60 min following anesthetic emergence in infants.

B. Respiratory

Sevoflurane depresses respiration and reverses bronchospasm to an extent similar to that of isoflurane.

C. Cerebral

Similar to isoflurane and desflurane, sevoflurane causes slight increases in CBF and intracranial pressure at normocarbia, although some studies show a decrease in cerebral blood flow. High concentrations of sevoflurane (>1.5 MAC) may impair autoregulation of CBF, thus allowing a drop in CBF during hemorrhagic hypotension. This effect on CBF autoregulation seems to be less pronounced than with isoflurane. Cerebral metabolic oxygen requirements decrease, and seizure activity has not been reported.

D. Neuromuscular

Sevoflurane produces adequate muscle relaxation for intubation of children following an inhalation induction.

E. Renal

Sevoflurane slightly decreases renal blood flow. Its metabolism to substances associated with impaired renal tubule function (eg, decreased concentrating ability) is discussed below.

F. Hepatic

Sevoflurane decreases portal vein blood flow, but increases hepatic artery blood flow, thereby maintaining total hepatic blood flow and oxygen delivery. It is generally not associated with immune-mediated anesthetic hepatotoxicity

Biotransformation & Toxicity

The liver microsomal enzyme P-450 (specifically the 2E1 isoform) metabolizes sevoflurane at a rate one-fourth that of halothane (5% versus 20%), but 10 to 25 times that of isoflurane or desflurane and may be induced with ethanol or phenobarbital pretreatment. The potential nephrotoxicity of the resulting rise in inorganic fluoride (F^-) was discussed earlier. Serum fluoride concentrations exceed 50 μmol/L in approximately 7% of patients who receive sevoflurane, yet clinically significant renal dysfunction has not been associated with sevoflurane anesthesia. The overall rate of sevoflurane metabolism is 5%, or 10 times that of isoflurane. Nonetheless, there has been no association with peak fluoride levels following sevoflurane and any renal concentrating abnormality.

Alkali such as barium hydroxide lime or soda lime (but not calcium hydroxide) can degrade sevoflurane, producing another proven (at least in rats) nephrotoxic end product (*compound A*, fluoromethyl-2,2-difluoro-1-[trifluoromethyl]vinyl ether). Accumulation of compound A increases with increased respiratory gas temperature, low-flow anesthesia, dry barium hydroxide absorbent (Baralyme), high sevoflurane concentrations, and anesthetics of long duration.

Most studies have not associated sevoflurane with any detectable postoperative impairment of renal function that would indicate toxicity or injury. Nonetheless, some clinicians recommend that fresh gas flows be at least 2 L/min for anesthetics lasting more than a few hours and that sevoflurane not be used in patients with preexisting renal dysfunction.

Sevoflurane can also be degraded into hydrogen fluoride by metal and environmental impurities present in manufacturing equipment, glass bottle packaging, and anesthesia equipment. Hydrogen fluoride can produce an acid burn on contact with respiratory mucosa. The risk of patient injury has been substantially reduced by inhibition of the degradation process by adding water to sevoflurane during the manufacturing process and packaging it in a special plastic container. The manufacturer has also distributed a "Dear Provider" letter warning of isolated incidents of fire in the respiratory circuits of anesthesia machines with desiccated CO_2 absorbent when sevoflurane was used.

Contraindications

Contraindications include severe hypovolemia, susceptibility to malignant hyperthermia, and intracranial hypertension.

Drug Interactions

Like other volatile anesthetics, sevoflurane potentiates NMBAs. It does not sensitize the heart to catecholamine-induced arrhythmias.

XENON

Xenon is a "noble" gas that has long been known to have anesthetic properties. It is an inert element that does not form chemical bonds. Xenon is scavenged from the atmosphere through a costly distillation process. It is an odorless, nonexplosive, naturally occurring gas with a MAC of .71 and a blood/gas coefficient of 0.115, giving it very fast onset and emergence parameters. As previously mentioned, xenon's anesthetic effects seem to be mediated by NMDA inhibition by competing with glycine at the glycine binding site. Xenon seems to have little effect on cardiovascular, hepatic, or renal systems and has been found to be protective against neuronal ischemia. As a natural element, it has no effect upon the ozone layer compared with another NMDA antagonist, nitrous oxide. Cost and limited availability have prevented its widespread use.

SUGGESTED READING

Banks P, Franks N, Dickinson R: Competitive inhibition at the glycine site of the *N*-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia ischemia. Anesthesiology 2010;112:614.

Bantel C, Maze M, Trapp S: Neuronal preconditioning by inhalational anesthetics. Anesthesiology 2009;11:986.

Cittanova M-L, Lelongt B, Verpont M-C: Fluoride ion toxicity in human kidney collecting duct cells. Anesthesiology 1996;84:428.

Coburn M, Maze M, Franks N: The neuroprotective effects of xenon and helium in an in vitro model of traumatic brain injury. Crit Care Med 2008;36:588.

De Hert S, Preckel B, Schlack W: Update on inhalational anaesthetics. Curr Opin Anaesthesiol 2009;22:491.

DiMaggio C, Sun L, Li G: Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg 2011; 113:1143.

Ebert TJ: Myocardial ischemia and adverse cardiac outcomes in cardiac patients undergoing noncardiac surgery with sevoflurane and isoflurane. Anesth Analg 1997;85:993.

Eger EI 2nd, Bowland T, Ionescu P, et al: Recovery and kinetic characteristics of desflurane and sevoflurane in volunteers after 8-h exposure, including kinetics of degradation products. Anesthesiology 1997;87:517.

Eger EI 2nd, Raines DE, Shafer SL, Hemmings HC Jr, Sonner JM: Is a new paradigm needed to explain how inhaled anesthetics produce immobility? Anesth Analg 2008;107: 832.

Ghatge S, Lee J, Smith I: Sevoflurane: an ideal agent for adult day-case anesthesia? Acta Anaesthesiol Scand 2003;47:917.

Ishizawa Y: General anesthetic gases and the global environment. Anesth Analg 2011; 112:213.

Jevtovic-Todorovic V: Pediatric anesthesia neurotoxicity: an overview of the 2011 Smart Tots panel. Anesth Analg 2011;113:965.

Jordan BD, Wright EL: Xenon as an anesthetic agent. AANA J 2010;78:387.

Loeckinger A, Kleinsasser A, Maier S, et.al: Sustained prolongation of the QTc interval after anesthesia with sevoflurane in infants during the first 6 months of life. Anesthesiology 2003;98:639.

Njoku D, Laster MJ, Gong DH: Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anesth Analg 1997;84:173.

Preckel B, Weber N, Sanders R, et al: Molecular mechanisms transducing the anesthetic analgesic and organ protective actions of Xenon. Anesthesiology 2006;105:187.

Stratmann G: Neurotoxicity of anesthetic drugs in the developing brain. Anesth Analg 2011;113:1170.

Summors AC, Gupta AK, Matta BF: Dynamic cerebral autoregulation during sevoflurane anesthesia: a comparison with isoflurane. Anesth Analg 1999;88:341.

Sun X, Su F, Shi Y, Lee C: The "second gas effect" is not a valid concept. Anesth Analg 1999;88:188.

Thomas J, Crosby G, Drummond J, et.al: Anesthetic neurotoxicity: a difficult dragon to slay. Anesth Analg 2011;113;969.

Torri G: Inhalational anesthetics: a review. Minerva Anestesiol 2010;76:215.

Wang L, Traystman R, Murphy S: Inhalational agents in ischemic brain. Curr Opin Pharmacol 2008;8:104.

Wei H: The role of calcium dysregulation in anesthetic mediated neurotoxicity. Anesth Analg 2011;113:972.