Chapter 13

Inhalation Anesthetics

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Introduction

Inhalation anesthetics are used widely for the anesthetic management of animals. They are unique among the anesthetic drugs because they are administered, and in large part removed from the body, via the lungs. Their popularity arises in part because their pharmacokinetic characteristics favor predictable and rapid adjustment of anesthetic depth. In addition, a special apparatus is usually used to deliver the inhaled agents. This apparatus includes a source of oxygen (O_2) and a patient breathing circuit that in turn usually includes an endotracheal tube or face mask, a means of eliminating carbon dioxide (CO_2), and a compliant gas reservoir. These components help minimize patient morbidity or mortality because they facilitate lung ventilation and improved arterial oxygenation. In addition, inhalation anesthetics in gas samples can now be readily and affordably measured almost instantaneously. Measurement of inhalation anesthetic concentration enhances the precision and safety of anesthetic management beyond the extent commonly possible with injectable anesthetic agents.

Over the nearly 150 years that inhalation anesthesia has been used in clinical practice, fewer than 20 agents have actually been introduced and approved for general use with patients (Fig. 13.1).[1] Fewer than ten of these have had any history of widespread clinical use in veterinary medicine, and only 5 are of current clinical veterinary importance in North America. It is this group of anesthetics that are the focus of this chapter. Isoflurane is generally considered the most widely used inhalation anesthetic in veterinary medicine, having replaced halothane in this regard. The gaseous agent nitrous oxide (N_2O) and the newest volatile agent sevoflurane, along with halothane, enjoy varying degrees of popularity and are grouped in an intermediary category. It is important to note that, at the time of updating this chapter, suppliers are considering no longer making and distributing halothane, at least in North America. However, because the decision at this time is not final, for purposes of this chapter, the author will continue to include information on halothane. The other newer volatile anesthetic, desflurane, is presently only of limited use in veterinary medicine but is grouped among the five contemporary agents. Two additional volatile agents receive brief attention for different reasons. Methoxyflurane, an agent popular during the period of about 1960 to 1990, is no longer commercially available in North America. However, because of some of its physical-chemical characteristics, mention here has value to the reader in comparing agents of more current interest. Enflurane, introduced for use in human patients in 1972 and still commercially available, has little or no use in veterinary practice in the United States but remains in limited use elsewhere for management of small companion animal patients or laboratory animals. Although of investigational interest, a review of xenon is not included in this clinically focused chapter.

In this edition, information on agents of largely historical interest has not been included. Readers interested in aspects of these formally used agents are referred to the earlier editions of this and other textbooks.[2–6] Such agents include diethyl ether, chloroform, and others noted in Fig. 13.1.

Physiochemical Characteristics

The chemical structure of inhalation anesthetics and their physical properties determine their actions and safety of administration. An in-depth analysis of the impact of agent chemical structure and physical properties is beyond the scope of this chapter. However, brief discussion of aspects of Fig. 13.2 and Table 13.1 is appropriate because the physiochemical characteristics summarized determine and/or influence practical considerations of

Inhalation Anesthetics in Clinical Practice

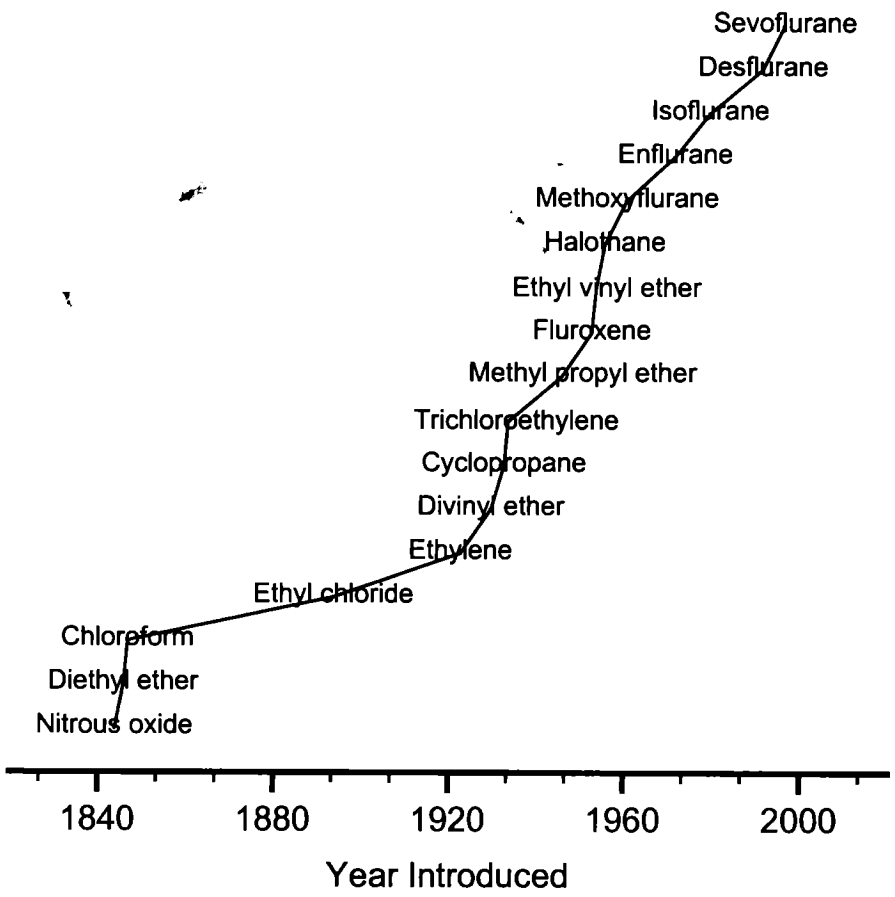


Fig. 13.1. Inhalation anesthetics introduced for widespread clinical use. Adapted from Eger[1] and Karzai et al.[323]

their clinical use. For example, they determine the form in which the agents are supplied by the manufacturer (i.e., as a gas or liquid) and account for the resistance of the anesthetic molecule to degradation by physical factors (e.g., heat and light) and substances it contacts during use (e.g., metal components of the anesthetic-delivery apparatus and the CO_2 absorbents such as soda lime). The equipment necessary to deliver the agent safely to patients (e.g., vaporizer and breathing circuit) is influenced by some of these properties, as are the agent's uptake, distribution within, and elimination (including potential for metabolic breakdown) from the patient. In summary, a knowledge and understanding of fundamental properties enable more intelligent use of contemporary anesthetics.

Chemical Characteristics

All contemporary inhalation anesthetics are organic compounds except N_2O (Fig. 13.2) (cyclopropane and xenon are other notable inorganic anesthetics). Agents of current interest are further classified as either aliphatic (i.e., straight or branch chained) hydrocarbons or ethers (i.e., two organic radicals attached to an atom of O_2; the general structure is ROR). In the continued search for a less reactive, more potent, nonflammable inhalation anesthetic, focus on halogenation (i.e., addition of fluorine, chlorine, or bromine; iodine is least useful) of these compounds has predominated. Chlorine and bromine especially convert many compounds of low anesthetic potency into more potent drugs. Historically, interest in fluorinated derivatives was delayed until the 1940s because of difficulties in synthesis, and thus quantities available for study were limited. Methods of synthesis, although difficult, have improved considerably and facilitated new agent discovery (Fig. 13.2). It is interesting that organic fluorinated compounds are a group of extreme contrasts—some are toxic, others are not; some are extremely inert, others are highly reactive. In some anesthetics, fluorine is substituted for chlorine or

Table 13.1. Some physical and chemical properties of inhalation anesthetics in current clinical use for animals

Property	Desflurane	Enflurane	Halothane	Isoflurane	Methoxyflurane[a]	N_2O	Sevoflurane
Molecular weight (g)	168	185	197	185	165	44	200
Liquid specific gravity (20°C) (g/mL)	1.47	1.52	1.86	1.49	1.42	1.42	1.52
Boiling point (°C)	23.5	57	50	49	105	−89	59
Vapor pressure (mm Hg)							
20°C	700[325]	172	243	240	23	—	160
24°C	804	207	288	286	28	—	183
mL vapor/mL liquid at 20°C	209.7	197.5	227	194.7	206.9	—	182.7
Preservative	None	None	Yes	None	Not available	None	Yes
Stability in							
Soda lime	Yes	Yes	No	Yes	No	Yes	No
Ultraviolet light	Yes	Yes	No	Yes	No	Yes	?

Excepting for new citations where noted, references appear in the immediate past edition of this text and chapter. N_2O, nitrous oxide.
[a]Methoxyflurane is no longer available.

bromine to improve stability but at the expense of reduced anesthetic potency and solubility.

Halothane (Fig. 13.2) is a halogenated, aliphatic saturated hydrocarbon (ethane). Predictions that halogenated structure would provide nonflammability and molecular stability encouraged the development of halothane in the early 1950s. However, soon after clinical introduction it was observed that the concurrent presence of halothane and catecholamines increased the incidence of cardiac arrhythmias, especially in human patients. An ether linkage in the molecule favors a reduced incidence of cardiac arrhythmias. Consequently, this chemical structure is a predominant characteristic of all agents developed or proposed for clinical use since the introduction of halothane (Fig. 13.2).

Despite many favorable characteristics and improvements over earlier anesthetics (Fig. 13.1) that included improved chemical stability, halothane is susceptible to decomposition. Accordingly, halothane is stored in dark bottles, and a very small amount of a preservative, thymol, is added to it to retard breakdown. Thymol is much less volatile than halothane and over time collects within the devices used to control delivery of the volatile anesthetic (i.e., vaporizers) and causes them to malfunction. To accomplish greater molecular stability, fluorine is substituted for chlorine or bromine in the anesthetic molecule. This chemical manipulation added shelf life to the substance and negated the need for additives such as thymol. Unfortunately, the fluorine ion is also toxic to some tissues (e.g., kidneys), which is of clinical concern if the parent compound (e.g., sevoflurane and, historically, most notably methoxyflurane) is not resistant to metabolism (Fig. 13.2).

Physical Characteristics

There is a constant interchange of respiratory gases (O_2 and CO_2) between cells and the external environment via blood. Inhalation anesthesia involves additional considerations whereby an anesthetic must be transferred under control from a container to sites of action in the central nervous system (CNS). Early in this process the agent is diluted to an appropriate amount (concentration) and supplied to the respiratory system in a gas mixture that contains enough O_2 to support life. The chain of events that ensues is influenced by many physical and chemical characteristics that can be quantitatively described (Tables 13.1 to 13.4). The practical clinical applications of these quantitative descriptions are reviewed here. Limited space does not permit in-depth review of all underlying principles, and readers interested in further background information are referred elsewhere.[7,8]

The physical characteristics of importance to our understanding of the action of inhalation anesthetics can be conveniently divided into two general categories: those that determine the means by which the agents are administered and those that help determine their kinetics in the body. This information is applied in the clinical manipulation of anesthetic induction and recovery and in facilitating changes in anesthetic-induced CNS depression in a timely fashion.

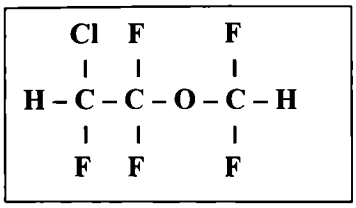
Properties Determining Methods of Administration

A variety of physical and chemical properties determine the means by which inhalation anesthetics are administered. These include characteristics such as molecular weight, boiling point, liquid density (specific gravity), and vapor pressure.

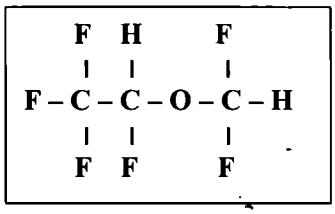
General Principles: A Brief Review Molecules are in a constant state of motion and exhibit a force of mutual attraction. The degree of attraction is evident by the state in which the substance exists (i.e., solid, liquid, or gas). Molecular motion increases as energy (e.g., in the form of heat) is added to the molecular aggregate and decreases as energy is removed. With increased motion the intermolecular forces are reduced; if conditions are extreme enough, a change in physical state may ensue. All substances exist naturally in a particular state but can be made to exist (at least in theory) in any or all phases by altering conditions. Water, as an example, exists as ice (mutual molecular attraction is great), liquid water, or water vapor (attraction considerably reduced), depending on conditions.

Gas versus Vapor Inhalation anesthetics are either gases or vapors. In relation to inhalation anesthetics the term *gas* refers to an agent, such as N_2O, that exists in its gaseous form at room tem-

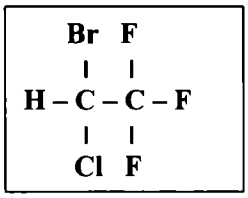
Enflurane
(Ethrane®)



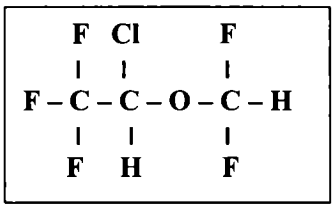
Desflurane
(Suprane®, 1653)



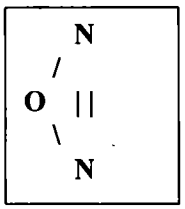
Halothane
(Fluothane®)



Isoflurane
(Forane®, Aerrane®)



Nitrous oxide



Sevoflurane
(Ultane®, Sevoflo®)

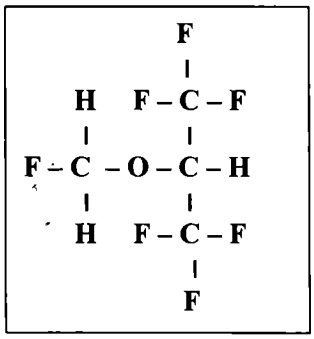


Fig. 13.2. Chemical structure of inhalation anesthetics in current use for animals. Trade names are in parentheses.

perature and sea level pressure. The term *vapor* indicates the gaseous state of a substance that at ambient temperature and pressure is a liquid. With the exception of N_2O, all the contemporary anesthetics fall into this category. Desflurane (Table 13.1) is one of the new volatile liquids that comes close to the transition stage and offers some unique (among the inhalation anesthetics) considerations to be discussed later in this chapter.

Whether inhalation agents are supplied as a gas or volatile liquid under ambient conditions, the same physical principles apply to each agent when it is in the gaseous state. Molecules move about haphazardly at high speeds and collide with each other (more frequently in liquid than in gas) or the walls of the containing vessel. The force of the bombardment is measurable and referred to as pressure. In the case of gases, if the space or volume in which the gas is enclosed is increased, the number of bombardments decreases (i.e., a smaller number of molecular collisions per unit time) and then the pressure decreases. The behavior of gases is predictably described by various gas laws. Relationships such as those described by Boyle's law (volume vs. pressure), Charles's law (volume vs. temperature), Gay-Lussac's law (temperature vs. pressure), and Dalton's Law of Partial Pressure (the total pressure of a mixture of gases is equal to the sum of the partial pressures of all of the gaseous substances present), among others, are important to our overall understanding of aspects of respiratory and anesthetic gases and vapors. However, in-depth descriptions of these principles are beyond the scope of this chapter, and readers are referred elsewhere for this information.[8]

Methods of Description Quantities of inhalation anesthetic agent are usually characterized by one of three methods: pressure (i.e., in millimeters of mercury [mm Hg]), concentration (in volume percent [vol%]) or mass (in milligrams [mg] or grams [g]). The form most familiar to clinicians is that of concentration (e.g., *X%* of agent A in relation to the whole gas mixture). Modern monitoring equipment samples inspired and expired gases and provides concentration readings for inhalation anesthetics. Precision vaporizers used to control delivery of inhalation anesthetics are calibrated in percentage of agent, and effective doses are almost always reported in percentages.

Pressure is also an important way of describing inhalation anesthetics and is further discussed as a measure of anesthetic potency. A mixture of gases in a closed container will exert a pressure on the walls of the container. The individual pressure of each gas in a mixture of gases is referred to as its *partial pressure*. As noted earlier, this expression of the behavior of a mixture of gases is known as Dalton's law, and its use in understanding inhalation anesthesia is inescapable. Use of the concept of partial pressure is important in understanding inhalation anesthetic action in a multiphase biological system because, unlike concentration, the partial pressure of an agent is the same in different compartments that are in equilibrium with each other. That is, in contradistinction to concentration or volume percent, an expression of the relative ratio of gas molecules in a mixture, partial pressure is an expression of the absolute value.

Molecular weight and agent density are used in many calculations to convert from liquid to vapor volumes and mass. Briefly

Table 13.2. Partition coefficients (solvent and gas) of inhalation anesthetics at 37°C

Solvent	Desflurane	Enflurane	Halothane	Isoflurane	Methoxyflurane	N_2O	Sevoflurane
Water	—	0.78	0.82	0.62	4.50	0.47	0.60
Blood	0.42	2.00	2.54	1.46	15.00	0.47	0.68
Olive oil	18.70	96.00	224.00	91.00	970.00	1.40	47.00
Brain	1.30	2.70	1.90	1.60	20.00	0.50	1.70
Liver	1.30	3.70	2.10	1.80	29.00	0.38	1.80
Kidney	1.00	1.90	1.00	1.20	11.00	0.40	1.20
Muscle	2.00	2.20	3.40	2.90	16.00	0.54	3.10
Fat	27.00	83.00	51.00	45.00	902.00	1.08	48.00

Tissue samples are derived from human sources. Data are from sources referenced in the immediate past edition of this text and chapter. N_2O, nitrous oxide.

Table 13.3. Solvent-gas partition coefficients for halothane at 37°C in a variety of species[327]

Solvent	Dog	Horse	Ox	Rabbit
Blood	3.51	1.77	2.40	4.02
Brain	6.03	5.42	4.80	6.22
Liver	6.64	8.51	5.10	9.17
Kidney	4.95	3.21	3.80	6.96
Muscle	5.45	3.55	5.40	3.67

Table 13.4. Rubber or plastic-gas partition coefficients at room temperature

Solvent	Desflurane	Enflurane	Halothane	Isoflurane	Methoxyflurane	N_2O	Sevoflurane	Reference
Rubber	—	74	120	62	630	1.2	—	Eger[1]
	19	—	190	49	—	—	29	Targ et al.[328]
Polyvinyl chloride	—	120	190	110	—	—	—	Eger[1]
	35	—	233	114	—	—	69	Targ et al.[328]
Polyethylene	—	~2	26	~2	118	—	—	Eger[1]
	16	—	128	58	—	—	31	Targ et al.[328]

These data are summarized from multiple sources as reported in Eger,[1] with some differences in methods of determination. The data from Targ et al.[328] indicate more recently derived data that, unlike earlier data, were recorded following complete equilibration with these materials. Where there is overlap, the ranking of partition coefficients is consistent with halothane > isoflurane > sevoflurane > desflurane. Combining both groupings yields methoxyflurane > halothane > enflurane > isoflurane > sevoflurane > desflurane > nitrous oxide.

(and in simplified fashion), Avogadro's principle is that equal volumes of all gases under the same conditions of temperature and pressure contain the same number of molecules (6.0226×10^{23} [Avogadro's number] per gram molecular weight). Furthermore, under standard conditions the number of gas molecules in a gram molecular weight of a substance occupies 22.4 L. To compare properties of different substances of similar state, it is necessary to do so under comparable conditions; with respect to gases and liquids this usually means with reference to pressure and temperature. Physical scientists have arbitrarily selected *standard conditions* as being 0°C (273 K in absolute scale) and 760 mm Hg pressure (1 atmosphere at sea level). If conditions differ, appropriate temperature and/or pressure corrections must be applied to resultant data.

The weight of a given volume of liquid, gas, or vapor may be expressed in terms of its density or specific gravity. The density is an absolute value of mass (usually grams) per unit volume (for liquids, volume = 1 mL; for gases, 1 L at standard conditions). The specific gravity is a relative value; that is, the ratio of the weight of a unit volume of one substance to a similar volume of water in the case of liquids or air in the case of gases (or vapors) under similar conditions. The value of both air and water is 1. At least for clinical purposes, the value for density and specific gravity for an inhalation anesthetic is the same. Thus, for example, we can determine the volume of isoflurane gas (vapor) at 20°C from a mL of isoflurane liquid according to the scheme given in Fig. 13.3. This type of calculation has practical applications. For example, to determine the savings in isoflurane liquid afforded by reducing the fresh gas (e.g., O_2) inflow rate, a series of calculations as presented in Fig. 13.4 can be made.

a. Isoflurane specific gravity = 1.49 g/mL, therefore:
1 mL liquid isoflurane = 1 mL x 1.49 g/mL = 1.49 g

b. Since molecular weight of isoflurane = 185 g (from Table 13-1, then:
1.49 g ÷ 185 g = 0.0081 mol of liquid

c. Since 1 mol of gas = 22.4 L, then:
0.0081 mol x 22,400 mL/mol = 181.4 mL of isoflurane vapor at 0C, 1 atm

d. But vapor is at 20C not 0C (i.e., 273 K),
So, 181.4 x 293/273 = 194.7 mL vapor/mL liquid isoflurane at 20C and at sea level pressure

For substantial variation in ambient pressure, the final figure noted above would have to be further "corrected" by a factor of: 760/ambient barometric pressure

Fig. 13.3. Example of calculations to determine the volume of isoflurane vapor at 20°C from 1 mL of isoflurane liquid.

a. Total isoflurane vapor delivered over 2 hours (120 min) estimated at:

3%/100 x 6 LPM = 0.18 LPM x 120 min = 21.60 L/120 min = 21,600 mL/120 min

vs

3%/100 x 4 LPM = 0.12 LPM x 120 min = 14.4 L/120 min = 14,400 mL/120 min

b. Total vapor volume saved:

21,600 mL/120 min – 14,400 mL/120 min = 7,200 mL vapor/120 min saved

c. Total liquid isoflurane volume saved/2 hours

7,200 mL vapor ÷ 194.7 mL vapor/mL liquid = 36.98 mL of isoflurane liquid

(194.7 mL vapor/mL liquid can be calculated as in Fig. 13.4 or taken from Table 13-1)

The economic value of reducing isoflurane consumption can then be determined by calculating the product of the liquid volume saved and the purchase cost/mL of isoflurane liquid

Fig. 13.4. Problem: Determine the savings in isoflurane liquid afforded by reducing the fresh gas (e.g., O_2) inflow rate from 6 Lpm (L/min) to 4 Lpm, given that the average delivered (vaporizer setting) concentration for 2 h is 3%.

Vapor Pressure Molecules of liquids are in constant random motion. Some of those in the surface layer gain sufficient velocity to overcome the attractive forces of neighboring molecules and in escaping from the surface enter the vapor phase. The change in state from a liquid to a gas phase is known as *vaporization* or *evaporation*. This process is dynamic and in a closed container that is kept at a constant temperature eventually reaches an equilibrium whereby there is no further net loss of

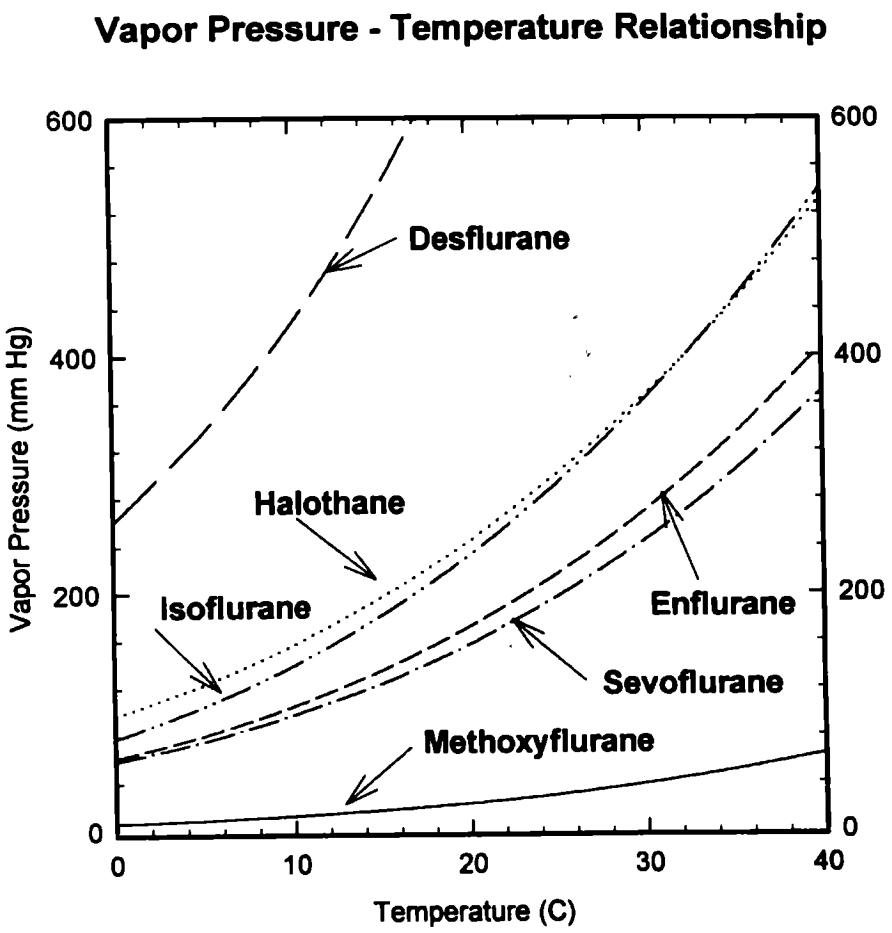


Fig. 13.5. Vapor pressure as a function of temperature for six volatile anesthetics. Curves are generated from Antoine equations.[324,325]

molecules to the gas phase (i.e., the numbers of molecules leaving and returning to the liquid phase are equal). The gas phase at this point is saturated.

Molecules of a vapor exert a force per unit area or pressure in exactly the same manner as do molecules of a gas. The pressure (mm Hg) that the vapor molecules exert when the liquid and vapor phases are in equilibrium is known as the *vapor pressure*. Thus, the vapor pressure of an anesthetic is a measure of its ability to evaporate; that is, it is a measure of the tendency for molecules in the liquid state to enter the gaseous (vapor) phase. The vapor pressure of a volatile anesthetic must be at least sufficient to provide enough molecules of anesthetic in the vapor state to produce anesthesia at ambient conditions. The *saturated vapor pressure* represents a maximum concentration of molecules in the vapor state that exists for a given liquid at each temperature. Herein lies a practical difference between substances classified as a gas or vapor: A gas can be administered over a range of concentrations from 0 to 100%, whereas the vapor has a ceiling that is dictated by its vapor pressure. The saturated vapor concentration can be easily determined by relating the vapor pressure to the ambient pressure. For example, in the case of halothane (Table 13.1), a maximal concentration of 32% halothane is possible under usual conditions (i.e., [244/760] × 100 = 32%, where 760 mm Hg is the barometric pressure at sea level). With other variables considered constant, the greater the vapor pressure, the greater is the concentration of the drug deliverable to a patient. Therefore, again from Table 13.1, halothane, for example, is more volatile than methoxyflurane under similar conditions. The barometric pressure also influences the final concentration of an agent. For example, in locations such as Denver, Colorado, where the altitude is about 5000 feet above sea level and the barometric pressure is only about 635 mm Hg, the saturated vapor concentration of halothane at 20°C is now (243/635) × 100 = 38.3%.

It is important to recognize that the saturated vapor pressure at 1 atmosphere is unique for each volatile anesthetic agent and depends only on its temperature. In this case, the effect of barometric pressure can be neglected over ranges normally encountered in the practice of anesthesia. Thus, for a given agent, the graph of the saturated vapor pressure versus temperature is a curve as shown in Fig. 13.5. From this graph it can be seen that if the temperature of the liquid is increased, more molecules escape the liquid phase and enter the gaseous phase. The greater number of molecules in the vapor phase produces a greater vapor pressure and vapor concentration. Conversely, if the liquid is cooled, the reverse occurs and vapor concentration decreases. Liquid cooling may occur not only because of changing ambient conditions but also as a natural consequence of the vaporization process. For example, during vaporization the "fastest" molecules at the surface escape first. With depletion of these "high energy" molecules, the average kinetic energy of those left behind is reduced, and there

is a tendency for the temperature of the remaining liquid to fall if this process is not compensated for externally. As the temperature decreases, the vapor pressure, and thus the vapor concentration, also decreases.

Boiling Point The *boiling point* of a liquid is defined as the temperature at which the vapor pressure of the liquid is equal to the atmospheric pressure. Customarily, the boiling temperature is stated at the standard atmospheric pressure of 760 mm Hg. The boiling point decreases with increasing altitude because the vapor pressure does not change, but the barometric pressure decreases. The boiling point of N_2O is −89°C (Table 13.1) at 1 atmosphere pressure at sea level. It is thus a gas under operating-room conditions. Because of this, it is distributed for clinical purposes in steel tanks compressed to the liquid state at about 750 psi (pounds per square inch; 750 psi/14.9 psi [1 atmosphere] = 50 atmospheres). As the N_2O gas is drawn from the tanks, liquid N_2O is vaporized, and the overriding gas pressure remains constant until no further liquid remains in the tank. At that point, only N_2O gas remains, and the gas pressure decreases from this point as remaining gas is vented from the tank. Consequently, the weight of the N_2O minus the weight of the tank, rather than the gas pressure within the tank, is a more accurate guide to the remaining amount of N_2O in the tank.[9]

Desflurane, the newest clinically available volatile anesthetic, also possesses an interesting consideration because its boiling point (Table 13.1) is near room temperature. This characteristic accounted for an interesting engineering challenge in developing an administration device (i.e., a vaporizer) for routine use in the relatively constant environment of the operating room and limits further consideration of its use in all but a narrow range of circumstances commonly encountered in veterinary medical applications. For example, because of its low boiling point, even evaporative cooling has large influences on vapor pressure and thus the vapor concentration of gas mixtures delivered to patients.

Calculation of Anesthetic Concentration Delivered by a Vaporizer The saturated vapor pressure of most volatile anesthetics is of such magnitude that the maximal concentration of anesthetic attainable at usual operating-room conditions is above the range of concentrations that are commonly necessary for safe clinical anesthetic management. Therefore, some control of the delivered concentration is necessary and usually provided by a device known as a *vaporizer*. The purpose of the vaporizer is to dilute the vapor generated from the liquid anesthetic with O_2 (or an O_2 and N_2O mixture) to produce a more satisfactory inspired-anesthetic concentration. This anesthetic dilution is usually accomplished as indicated in the Fig. 13.6 model by diverting the gas entering the vaporizer into two streams, one that enters the vaporizing chamber (anesthetic chamber volume: V_{anes}) and the other that bypasses the vaporizing chamber (dilution volume or $V_{dilution}$). If the vaporizer is efficient, the carrier gas passing through the vaporizing chamber becomes completely saturated to an anesthetic concentration (%) reflected by (anesthetic-agent vapor pressure/atmospheric pressure) × 100, at the vaporizer chamber temperature. The resultant anesthetic concentration then is decreased (diluted) downstream by the second gas stream to a "working" concentration. In modern, precision, agent-specific vaporizers no mental effort is required—just set the dial; the manufacturers have precalibrated the vaporizer for accurate delivery of the dialed concentration. Nevertheless, it is helpful to our overall understanding to know the principles underlying this convenience and how to apply these principles in the use of older noncompensated measured-flow vaporizers.

To calculate the anesthetic concentration from the vaporizer, one must know the vapor pressure of the agent (at the temperature of use), the atmospheric pressure, the fresh gas flow entering the vaporizing chamber, and the diluent gas flow. Then,

$$\% \text{ anesthetic} = \text{flow of anesthetic from the vaporizing chamber/total gas flow}$$

More detail for interested readers is presented in Fig. 13.6.

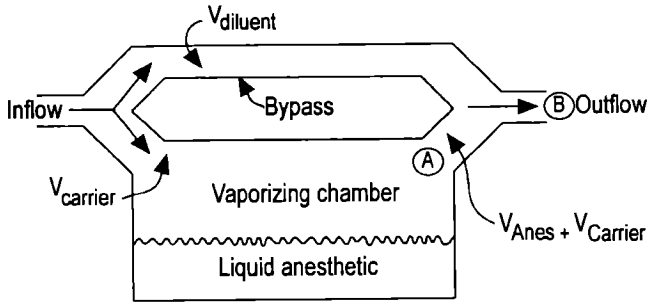
Properties Influencing Drug Kinetics: Solubility

Anesthetic gases and vapors dissolve in liquids and solids. The solubility of an anesthetic is a major characteristic of the agent and has important clinical ramifications. For example, anesthetic solubility in blood and body tissues is a primary factor in the rate of uptake and its distribution within the body. It is therefore a primary determinant of the speed of anesthetic induction and recovery. Solubility in lipid bears a strong relationship to anesthetic potency, and its tendency to dissolve in anesthetic-delivery components such as rubber goods influences equipment selection and other aspects of anesthetic management.

Solubility of Gases As previously mentioned, molecules of a gas that overlie a liquid surface are in random motion, and some penetrate the liquid surface. After entering the liquid they intermingle with the molecules of the liquid (i.e., the gas dissolves in the liquid). There is a net movement of the gas into the liquid until equilibrium is established between the dissolved gas in the liquid and the undissolved portion above the liquid. At this time there is no further net gain of gas molecules by the liquid, and the number of gas molecules entering the liquid equals the number leaving. The gas molecules within the liquid exert the same pressure or tension that they exert in the gas phase. If the pressure (i.e., the number of gas molecules overlying the liquid) is increased, more molecules pass into the liquid, and the pressure within the liquid is increased. This net inward movement of gas molecules continues until a new equilibrium is established between the pressure of the gas in the liquid and that overlying the liquid. Alternatively, if the pressure of gas overlying the liquid is somehow decreased below that in the liquid, gas molecules escape from the liquid. This net outward movement of gas molecules from the liquid phase continues until equilibrium between the two phases is reestablished.

The amount, that is, the total number of molecules of a given gas dissolving in a solvent depends on the chemical nature of the gas itself, the partial pressure of the gas, the nature of the solvent, and the temperature. This relationship is described by Henry's law,

$$V = S \times P$$



Steps:

1. The saturated *concentration* of anesthetic in the anesthetic vaporizing chamber and leaving it (ideally at A above) is calculated knowing the saturated vapor pressure (P_{VP}) (from Table 2) and barometric pressure (P_B).

   For example:

$$\text{Halothane\%} = \frac{243}{760} \times 100 = 32.0\% \qquad \text{(a)}$$

2. The *volume* of anesthetic leaving the vaporizing chamber is the original volume of the carrier gas (O_2) entering the anesthetic vaporizing chamber ($V_{carrier}$) and the volume of anesthetic (V_{halo}) added to it.

$$\text{Halothane\%} = \frac{V_{halo}}{V_{carrier} + V_{halo}} \times 100 \qquad \text{(b)}$$

   Halothane% is known from (a) above and $V_{carrier}$ is known from control of a flowmeter (e.g., a measured flow vaporizer) or via the design characteristics of a commercial, agent-specific, vaporizer that automatically "splits" the fresh gas flow from a single flow meter. In the first case, two gas flow controls are necessary, one for $V_{carrier}$ and one for a larger gas dilution flow ($V_{dilution}$). In either the case of manual or automatic fresh gas flow alteration, the equation is then solved for V_{halo} (expressed in ml of halothane vapor).

   For example, if $V_{carrier}$ = 100 mL O_2, then

$$32\% = \frac{V_{halo}}{100 + V_{halo}} \times 100$$

$$3200 + 32V_{halo} = 100V_{halo}$$

$$3200 = 68V_{halo}$$

$$V_{halo} = 47.1 \text{ mL halothane vapor}$$

3. V_{halo} is then contained in a total gas volume at B of

$$V_{total\ gas} = V_{halo} + V_{carrier} + V_{diluent} \qquad \text{(c)}$$

   Where $V_{diluent}$ is set by the anesthetist using a second gas control (i.e., flowmeter; units here of mL/min) or by the vaporizer design and dial setting.

   Then in our example for a $V_{diluent}$ of 1000 mL (in 1 minute)

$$V_{total} = 47.1 + 100 + 1000$$

$$= 1147 \text{ ml (rounded off)}$$

4. So the final halothane vapor concentration is determined by

$$\text{halothane \%} = \frac{V_{halo}}{V_{Total}} \times 100$$

   Again, in our example,

$$\text{halothane \%} = \frac{47.1}{1147} = 4.1\%$$

   Alternatively, with some basic algebraic work with equations given above, the same numbers can be applied to the resultant formula given below to arrive at the anesthetic concentration. The condensed formula is:

$$\text{Anesthetic concentration (\%)} = \frac{V_{carrier} \cdot P_{VP} \cdot 100}{V_{diluent} \cdot (P_B - P_{VP}) + (V_{carrier} \cdot P_B)}$$

Fig. 13.6. An anesthetic vaporizer model to assist in illustrating the principles associated with the calculation of the vapor concentration of an inhalation anesthetic emerging from a vaporizer. Conditions associated with halothane delivery in San Francisco (i.e., at sea level; barometric pressure = 760 mm Hg) at 20°C are used as an example of general principles.

where V is the volume of gas, P is the partial pressure of the gas, and S is the solubility coefficient for the gas in the solvent at a given temperature. Henry's law applies to gases that do not combine chemically with the solvent to form compounds.

Before leaving this basic information, a brief focus on a number of variations may be helpful. First, it is important to recognize that if the atmosphere that overlies the solvent is made up of a mixture of gases, then each gas dissolves in the solvent in proportion to the partial pressure of the individual gases. The total pressure exerted by the molecules of all gases within the solvent equals the total gas pressure lying above the solvent.

Within the body there is a partition of anesthetic gases between blood and body tissues in accordance with Henry's law. This process can be perhaps better understood by visualizing a system composed of three compartments (e.g., gas, water, and oil) contained in a closed container (Fig. 13.7). In such a system the gas overlies the oil, which in turn overlies the water. Because there is a passive gradient from the gas phase to the oil, gas molecules move into the oil compartment. This movement in turn develops a gradient for the gas molecules in oil relative to water. If gas is continually added above the oil, there will be a continual net movement of the gas molecules from the gas phase into both the oil and, in turn, the water. At a given temperature, when no more gas dissolves in the solvent, the solvent is said to be *fully saturated*. At this point the pressure of the gas molecules within the three compartments will be equal, but the amount (i.e., the number of molecules or volume of gas) partitioned between the two liquids will vary with the nature of the liquid and gas. Finally, it is important to understand that the amount of gas that goes into solution depends on the temperature of the solvent. Less gas dissolves in a solvent as temperature increases, and more gas is taken up as solvent temperature decreases. For example, as water is heated, air bubbles appear inside the container as a result of the decreasing solubility of the air in water.

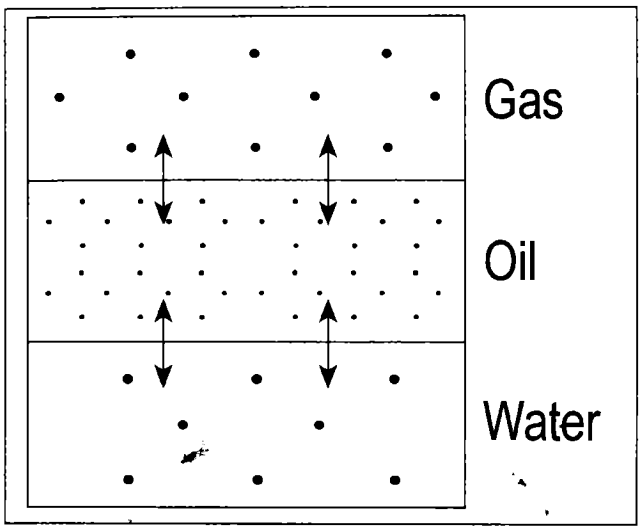


Fig. 13.7. Diagrammatic representation of an anesthetic gas distributing itself among three compartments (gas, oil, and water). At equilibrium, the number of anesthetic molecules in the three compartments differs, but the pressure exerted by the anesthetic molecules is the same in each compartment.

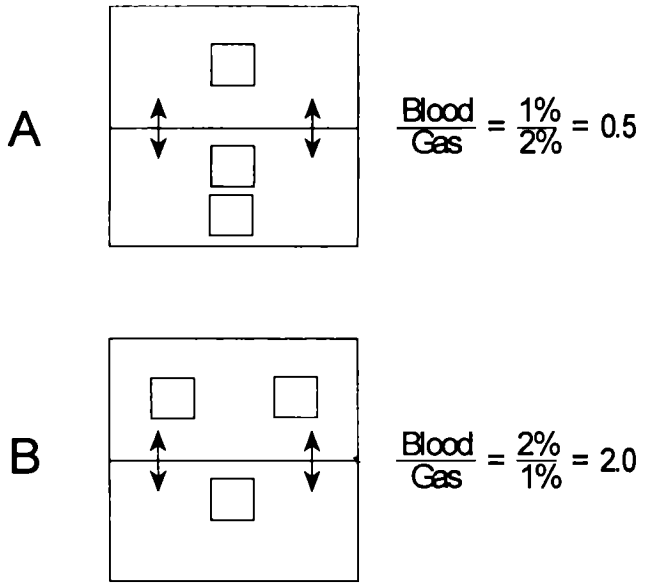


Fig. 13.8. Blood-gas partition coefficient illustration. Adapted from Eger.[10]

Conversely, as blood is cooled from a normal body temperature (e.g., hypothermia), gases become more soluble in blood.

The extent to which a gas will dissolve in a given solvent is usually expressed in terms of its solubility coefficient (Table 13.2). With inhalation anesthetics, solubility is most commonly measured and expressed as a *partition coefficient* (PC). Other measurements of solubility include the Bunsen and Ostwald solubility coefficients.[8,10]

The PC is the concentration ratio of an anesthetic in the solvent and gas phases (e.g., blood and gas) (Fig. 13.8) or between two tissue solvents (e.g., brain and blood) (Table 13.2). It thus describes the capacity of a given solvent to dissolve the anesthetic gas; that is, how the anesthetic will *partition* itself between the gas and the liquid solvent phases after equilibrium has been reached. Remember, anesthetic gas movement occurs because of a partial pressure difference in the gas and liquid solvent phases, so when there is no longer any anesthetic partial pressure difference there is no longer any net movement of anesthetic, and equilibrium has been achieved. Solvent-gas PCs are summarized in Table 13.2. The values noted in this table are for human tissues because these values are most widely available in the anesthesia literature. Comparative data for halothane with some species of clinical interest in veterinary medicine is listed in Table 13.3. Regardless of the species, it is important to emphasize that many factors can alter anesthetic-agent solubility.[10–13] Perhaps the most notable after the nature of the solvent is temperature.

Of all the PCs that have been described or are of interest, two are of particular importance in the practical understanding of anesthetic action. They are the blood-gas and the oil-gas solubility coefficients.

Blood-Gas Partition Coefficient Blood-gas solubility coefficients (Tables 13.2 and 13.3) provide a means for predicting the speed of anesthetic induction, recovery, and change of anesthetic depth. Assume, for example, that anesthetic A has a blood-gas PC value of 15. This means that the concentration of the anesthetic in blood will be 15 times greater at equilibrium than that in alveolar gas. Expressed differently, the same volume of blood, say 1 mL, will hold 15 times more of anesthetic A than 1 mL of alveolar gas despite an equal partial pressure. Alternatively, consider anesthetic B with a PC of 1.4. This PC indicates that, at equilibrium, the amount of anesthetic B is only 1.4 times greater in blood than it is in alveolar air. Comparing the PC of anesthetic A with that of anesthetic B indicates that anesthetic A is much more soluble in blood than B (nearly 11 times more soluble: 15/1.4). From this, and assuming other conditions are equal, anesthetic A will require a longer time of administration to attain a partial pressure in the body for a particular end point (say, anesthetic induction) than will anesthetic B. Also, since there is more of anesthetic A contained in blood and other body tissues under similar conditions, elimination (and therefore anesthetic recovery) will be prolonged when compared with anesthetic B.

Oil-Gas Partition Coefficient The oil-gas PC is another solubility characteristic of clinical importance (Table 13.2). This PC describes the ratio of the concentration of an anesthetic in oil (olive oil is the standard) and gas phases at equilibrium. The oil-gas PC correlates directly with anesthetic potency (see the section Anesthetic Dose: The Minimum Alveolar Concentration) and describes the capacity of lipids for anesthetic.

Other Partition Coefficients Solubility characteristics for various tissues (Tables 13.2 and 13.3) and other media, such as rubber

and plastic (Table 13.4), are also important. For example, the solubility of a tissue determines in part the quantity of anesthetic removed from the blood to which it is exposed. The higher the tissue solubility, the longer it will take to saturate the tissue with anesthetic agent. Thus, other things considered equal, anesthetics that are very soluble in tissues will require a longer period for induction and recovery. If the amount of rubber goods in the apparatus used to deliver the anesthetic to a patient is substantial, and the anesthetic-agent solubility in rubber is large, the amount of uptake of anesthetic agent by the rubber may be of clinical significance.

Pharmacokinetics: Uptake and Elimination of Inhalation Anesthetics

The aim in administering an inhalation anesthetic to a patient is to achieve an adequate partial pressure or tension of anesthetic (P_{anes}) in the CNS (e.g., brain; for purposes of this discussion, considerations of anesthetic delivery to spinal cord sites of action are considered similar to those of the brain) to cause a desired level of CNS depression commensurate with the definition of general anesthesia. Anesthetic depth varies directly with P_{anes} in brain tissue. The rate of change of anesthetic depth is of obvious clinical importance and depends directly on the rate of change in anesthetic tensions in the various media in which it is contained before reaching the brain. Thus, knowledge of the factors that govern these relationships is of fundamental importance to skillful control of general inhalation anesthesia.

Inhalation anesthetics are unique among the classes of drugs that are used to produce general anesthesia because they are administered via the lungs. The pharmacokinetics of the inhaled anesthetics describe the rate of their uptake by blood from the lungs, distribution in the body, and eventual elimination by the lungs and other routes. Readers seeking more in-depth coverage are directed to reviews by Eger,[10,14] Eger et al.,[15] and Mapleson.[16]

Inhalation anesthetics, similar to the gases of respiration (i.e., O_2 and CO_2), move down a series of partial pressure gradients from regions of higher tension to those of lower tension until equilibrium (i.e., equal pressure throughout the apparatus and body tissues) is established. Thus on induction, the P_{anes} at its source in a vaporizer is high, as is dictated by the vapor pressure, and progressively decreases as anesthetic travels from vaporizer to patient breathing circuit, from circuit to lungs, from lungs to arterial blood, and, finally, from arterial blood to body tissues (e.g., the brain) (Fig. 13.9). Of these the alveolar partial pressure (P_A) of anesthetic is pivotal. The brain has a rich blood supply, and the anesthetic in arterial blood (P_aAnes) rapidly equilibrates with brain tissue (P_{brain}Anes). Usually gas exchange at the alveolar level is sufficiently efficient that the P_aAnes is close to P_AAnes. Thus, the P_{brain}Anes closely follows P_AAnes, and by controlling the P_AAnes there is a reliable indirect way for controlling P_{brain}Anes and anesthetic depth.

At this point it may be also helpful to recall that although the partial pressure of anesthetic is of primary importance, we frequently define clinical dose of an inhaled anesthetic in terms of concentration (C; i.e., vol%). As previously noted this is because it is common practice for clinicians to regulate and/or measure

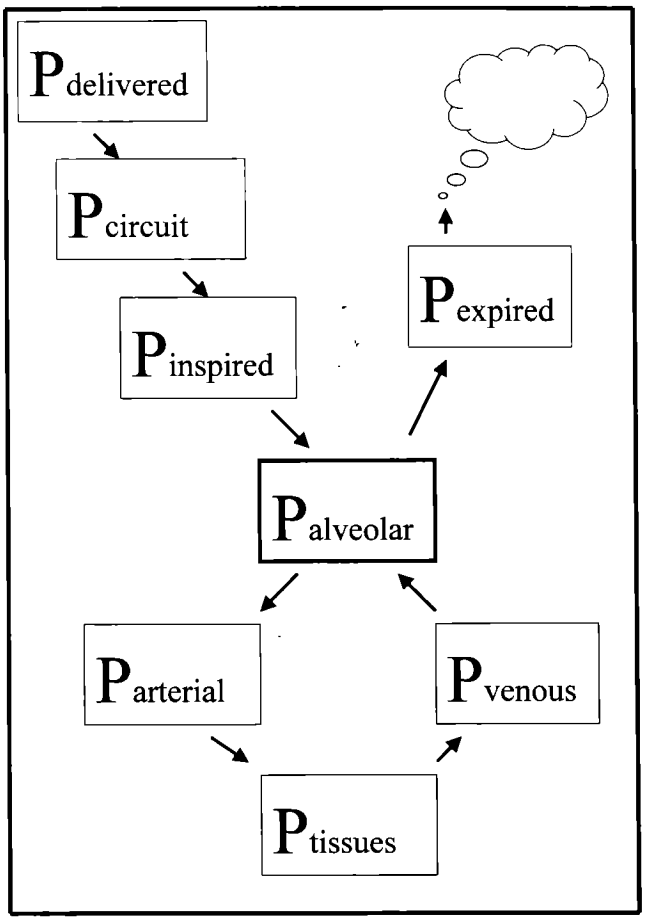


Fig. 13.9. The flow pattern of inhalation anesthetic agents during anesthetic induction and recovery. Inhalation anesthesia may be viewed as the development of a series of partial pressure (tension) gradients. During induction there is a high anesthetic tension in the vaporizer that decreases progressively as the flow of anesthetic gas moves from its source to the brain. Some of these gradients are easily manipulated by the anesthetist; others are not or are done so with difficulty.

respiratory and anesthetic gases in volume percent. In addition, in the gaseous phase, the relationship between the P_{anes} and the C_{anes} is a simple one:

$$P_{anes} = \text{fractional anesthetic concentration} \times \text{total ambient pressure}$$

The fractional anesthetic concentration is of course $C_{anes}/100$. However, as reviewed in the preceding section, in blood or tissues the actual *quantity* of anesthetic depends on both the P_{anes} and the anesthetic solubility (as measured by PC) within the solvent (e.g., blood or oil). Consequently, at equilibrium, the *partial pressure* of the gas in the alveoli and among tissue compartments will be equal although *concentrations* will vary within these tissues.

Anesthetic Uptake

The P_A of anesthetic is a balance between anesthetic input (i.e., delivery to the alveoli) and loss (uptake by blood and body tissues) from the lungs. A rapid rise in the P_A of anesthetic is asso-

A. Increased alveolar delivery
   1. Increased inspired anesthetic concentration
      a. Increased vaporization of agent
      b. Increased vaporizer dial setting
      c. Increased fresh gas inflow
      d. Decreased gas volume of patient breathing circuit
   2. Increased alveolar ventilation
      a. Increased minute ventilation
      b. Decreased dead space ventilation
B. Decreased removal from the alveoli
   1. Decreased blood solubility of anesthetic
   2. Decreased cardiac output
   3. Decreased alveolar-venous anesthetic gradient

Fig. 13.10. Factors related to a change in alveolar anesthetic tension (P_A, alveolar partial pressure).

ciated with a rapid anesthetic induction or change in anesthetic depth. Factors that contribute to a rapid change in the P_A of anesthetic are summarized in Fig. 13.10.

Delivery to the Alveoli

Delivery of anesthetic to the alveoli and therefore the rate of rise of the alveolar concentration or fraction (F_A) toward the inspired concentration or fraction (F_I) depends on the inspired-anesthetic concentration itself and the magnitude of alveolar ventilation. Increasing either one of these or both increases the rate of rise of the P_A of anesthetic; that is, with other things considered equal there is an increase in speed of anesthetic induction or change in anesthetic level.

Inspired Concentration The inspired concentration has a number of variables controlling it. First of all, the upper limit of inspired concentration is dictated by the agent vapor pressure, which in turn depends on temperature. This may be especially important considering the breadth of veterinary medical application of inhaled anesthesia and methods of vaporizing volatile anesthetics under widely diverse conditions (some environmental conditions are quite hostile).

Characteristics of the patient breathing system can also be a major factor in generating a suitable inspired concentration under usual operating-room conditions. Characteristics of special importance include the volume of the system, the amount of rubber or plastic components of the system, the position of the vaporizer relative to the breathing circuit (i.e., within or outside of the circuit), and the fresh gas inflow to the patient breathing circuit. The patient breathing circuit contains a gas volume that must be replaced with gas containing the desired anesthetic concentration. Thus, the volume of the breathing circuit serves as a buffer to delay the rise of anesthetic concentration. In the management of small animals (i.e., animals weighing less than 10 kg) a nonrebreathing patient circuit and/or a relatively high fresh gas inflow into the patient breathing circuit is usually used, so there should *not* be a clinically important difference between the delivered (e.g., vaporizer dial setting) and the inspired concentrations. That is, when the vaporizer dial setting is adjusted to the desired concentration setting, the fresh gas plus anesthetic flowing from the vaporizer almost immediately contains the dialed anesthetic vapor concentration. In addition, the total gas flow is high relative to the volume of the delivery circuit, so the anesthetic concentration in the inspired breath is rapidly increased. However, with animals weighing more than 10 kg, a circle, CO_2 absorber (i.e., rebreathing), patient breathing circuit is most commonly used for inhalation anesthesia. The volume of this breathing circuit may be very large compared with fresh gas inflow. This volume markedly delays the rate of rise of inspired-anesthetic concentration because the residual gas volume must be "washed out" and replaced by anesthetic containing fresh gas in order for the inspired concentration to increase to that delivered from the vaporizer (Fig. 13.11). In addition, exhaled gas (minus CO_2) is rebreathed to varying degrees with these circuits. The inspired gas is composed of exhaled and fresh gases. Because the expired gas contains less anesthetic than does the fresh gas, the inspired-anesthetic gas concentration

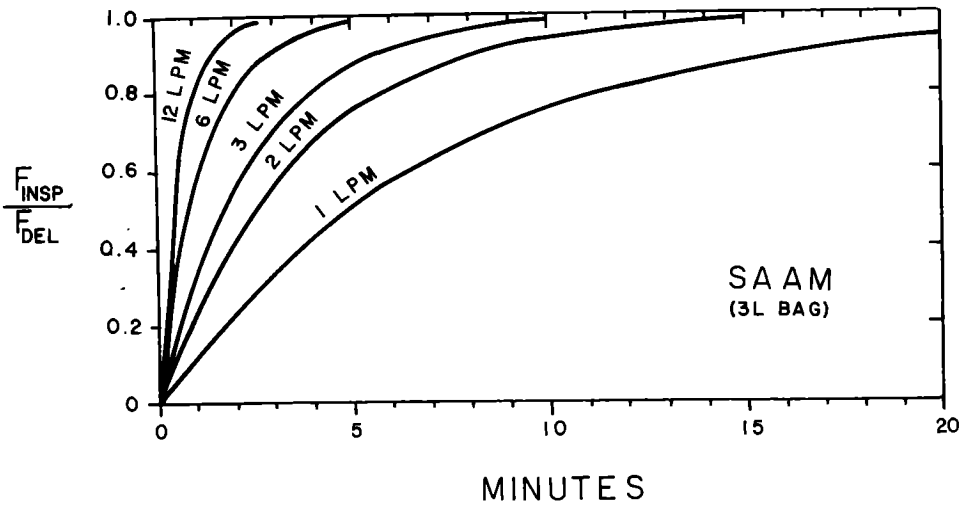


Fig. 13.11. A comparison of the rate of increase of inspired-halothane concentration toward a constant-delivered concentration F_{insp}/F_{del} in a 7-L small animal anesthetic breathing circuit (SAAM) at fresh gas flow rates of 1, 3, 6, and 12 L/min (LPM).[17]

Table 13.5. Vaporizer positioning within or outside of a circle patient rebreathing circuit influences inspired anesthetic concentration

	Vaporizer Positioning	
Factor	**Out of Circuit**	**In Circuit**
Increase ventilation	Decrease	Increase
Increase fresh gas (O_2) inflow to circuit	Increase	Decrease

will be less than that of the fresh gas leaving the vaporizer.

In veterinary applications, the delaying influence of the circle circuit is most notable with anesthetic management of very large animals such as horses[17] and cattle and/or when using a closed-circuit fresh gas flow rate (i.e., where O_2 is the fresh gas, and its inflow [plus anesthetic] to the circuit just meets the metabolic needs of the patient). With closed-circuit delivery, the fresh gas inflow is very low relative to the circuit volume.[7,10,17]

The high solubility of some older anesthetics (e.g., methoxyflurane) (Table 13.4) in rubber and plastic also delays development of an appropriate inspired-anesthetic concentration. The loss of anesthetic to these equipment "sinks" serves to increase the apparent volume of the anesthetic circuitry and may, in some cases, be clinically important (e.g., the use of rubber hoses and a large rubber rebreathing bag on circuits designed for anesthetic management of horses). With the newest inhalation anesthetics and more modern anesthetic-delivery equipment this issue is of minor or no clinical importance.

Positioning the vaporizer in relation to the patient breathing circuit will influence inspired-anesthetic concentration.[16,18] For example, with the vaporizer positioned within a circle rebreathing circuit, a decrease in inspired concentration will follow an increase in fresh gas inflow to the circuit, whereas an increase in inspired concentration will result if the vaporizer is positioned outside the circuit (Table 13.5). With the loss of methoxyflurane to clinical practice most vaporizers in use, at least in North America, are agent-specific, precision vaporizers. This style of vaporizer is always placed upstream and outside of the patient breathing circuit.

Alveolar Ventilation An increase in alveolar ventilation increases the rate of delivery of inhalation anesthetic to the alveolus (Fig. 13.12). If unopposed by blood and tissue uptake of anesthetic, alveolar ventilation would rapidly increase the alveolar concentration of anesthetic so that within minutes the alveolar concentration would equal the inspired concentration. However, in reality the input created by alveolar ventilation is countered by absorption of anesthetic into blood. Predictably, hypoventilation decreases the rate at which the alveolar concentration increases over time compared with the inspired concentration (i.e., anesthetic induction is slowed). Alveolar ventilation is altered by changes in anesthetic depth (increased depth usually means decreased ventilation), mechanical ventilation (usually increased ventilation), and dead-space ventilation (i.e., for any constant minute ventilation, a decrease in dead-space ventilation results in an increase in alveolar ventilation).

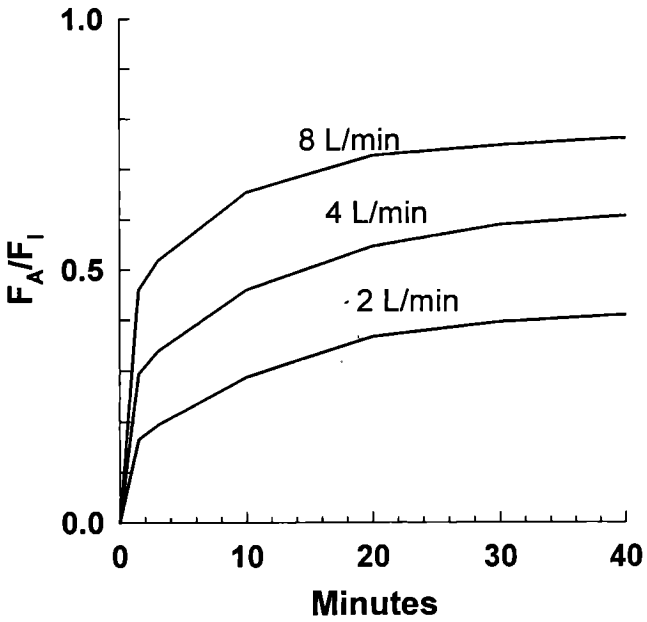


Fig. 13.12. The effect of ventilation on the rise of the alveolar concentration (F_A) of halothane toward the inspired (F_I) concentration. As noted, the F_A/F_I ratio increases more rapidly as ventilation is increased from 2 to 8 L/min. Redrawn from Eger,[10] with permission.

Alveolar ventilation and thus the alveolar anesthetic concentration can also be influenced by administering a potent inhalation anesthetic like halothane in conjunction with N_2O. Very early in the administration of N_2O (during the period of large volume uptake; the first 5 to 10 min of delivery) the rate of rise of the alveolar concentration of the concurrently administered inhalation anesthetic is increased. This is commonly referred to as the *second gas effect*, and this phenomenon can be applied clinically to speed anesthetic induction.[10,14,19]

Removal from Alveoli: Uptake by Blood

As noted by Eger,[10] anesthetic uptake is the product of three factors: solubility (S, the blood-gas solubility [Table 13.4]), cardiac output (CO), and the difference in the anesthetic partial pressure between the alveolus and venous blood returning to the lungs ($P_A - P_I$), expressed in mm Hg:

$$\text{uptake} = S \times CO(P_A - P_I/P_{bar})$$

where P_{bar} = barometric pressure in mm Hg. Note that if any of these three factors equals zero there is no further uptake of anesthetic by blood.

Solubility As previously discussed the solubility of an inhalation anesthetic in blood and tissues is characterized by its PC (Tables 13.2 and 13.3). Remember that a PC describes how an in-

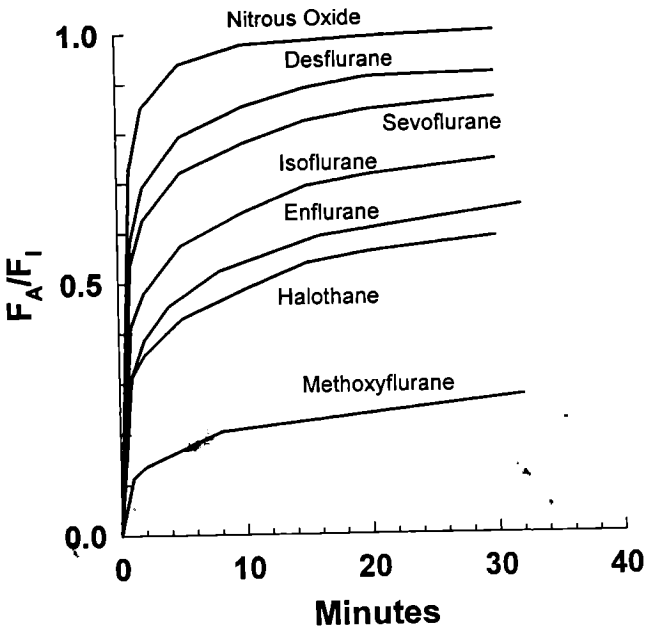


Fig. 13.13. The rise in the alveolar anesthetic concentration (F_A) toward the inspired concentration (F_I). Note that the rise is most rapid with the least soluble anesthetic, nitrous oxide, and slowest with the most soluble anesthetic, methoxyflurane. All data are from studies in people. The curves are redrawn from Eger.[1,326]

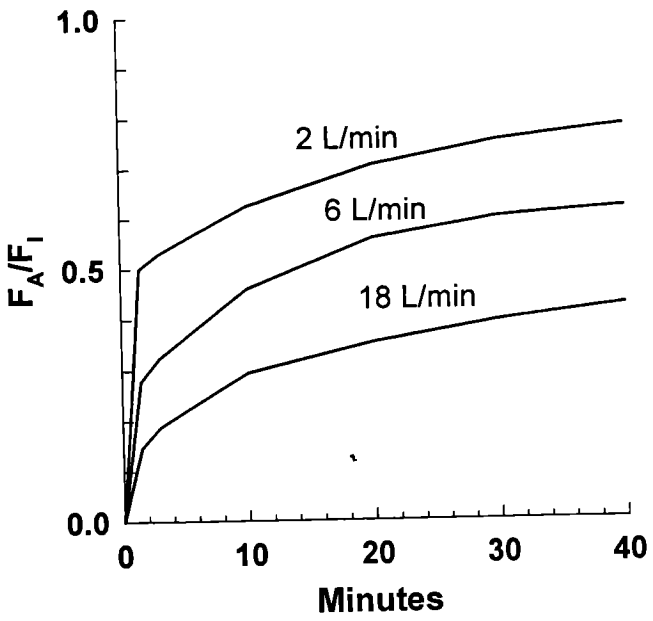


Fig. 13.14. The effect of cardiac output on the rise of the alveolar concentration (F_A) of halothane toward the inspired concentration (F_I). As noted, the F_A/F_I ratio increases more rapidly as cardiac output is decreased from 18 to 2 L/min. Redrawn from Eger.[10]

halation anesthetic distributes itself between two phases or two solvents (e.g., the quantity of agent in blood and alveoli [gas] or blood and muscle, respectively) once equilibrium is established (i.e., when the anesthetic partial pressure is equal). Based on blood-gas PCs, inhalation anesthetics range from highly soluble (methoxyflurane) to poorly soluble (N_2O, desflurane, and sevoflurane). Agents such as halothane and isoflurane are intermediary.

Compared with an anesthetic with high blood solubility (PC), an agent with low blood solubility is associated with a more rapid equilibration because a smaller amount of anesthetic must be dissolved in the blood before equilibrium is reached with the gas phase. In the case of the agent with a high blood-gas PC the blood acts like a large "sink" into which the anesthetic is poured, and accordingly blood is "reluctant" to give up the agent to other tissues (such as the brain). The blood serves as a conduit for drug delivery to the brain and as such can be visualized as a pharmacologically inactive reservoir that is interposed between the lungs and the agent's site of desired pharmacological activity (i.e., brain). Therefore, an anesthetic agent with a low blood-gas PC is usually more desirable than a highly soluble agent, because it is associated with (a) a more rapid anesthetic induction (i.e., more rapid rate of rise in alveolar concentration during induction [Fig. 13.13]); (b) a more precise control of anesthetic depth (i.e., alveolar concentration during the anesthetic maintenance); and (c) a more rapid elimination of anesthetic and recovery (i.e., a rapid decrease in alveolar concentration during recovery).

Cardiac Output The amount of blood flowing through the lungs and into body tissues also influences anesthetic uptake from the lungs. The greater the CO, the more blood is passing through the lungs carrying away anesthetic from the alveoli. Thus, a large CO, like increased anesthetic-agent blood solubility, delays the alveolar rise of P_{anes} (Fig. 13.14). Patient excitement is an example in which a relatively large CO is anticipated. Conversely, a reduced CO should be anticipated with a patient in shock. Such a situation would be associated with an increase in the rate of the P_A increase of the anesthetic, and this, along with other factors, make the anesthetic induction more rapid and risky.

Alveolar to Venous Anesthetic Partial Pressure Difference The magnitude of difference in anesthetic partial pressure between the alveoli and mixed venous blood is related to the amount of uptake of anesthetic by tissues. It is not surprising that the largest gradient occurs during induction. Once the tissues no longer absorb anesthetic (i.e., equilibrium is reached), there is no longer any uptake of anesthetic from the lungs because $P_I = P_A$ (i.e., the mixed venous blood returning to the lungs contains as much anesthetic as when it left the lungs). The changes in gradient between the initiation of induction and equilibration result in part from the relative distribution of CO. In this regard it is important to recognize that roughly 70% to 80% of the CO is normally directed to only a small volume of body tissues in a lean individual.[20,21] Tissues such as the brain, heart, hepatoportal system, and kidneys represent only about 10% of the body mass but normally receive about 75% of the total blood flow each minute. As a result these highly perfused tissues equilibrate rapidly with arterial anesthetic partial pressure when compared with other body

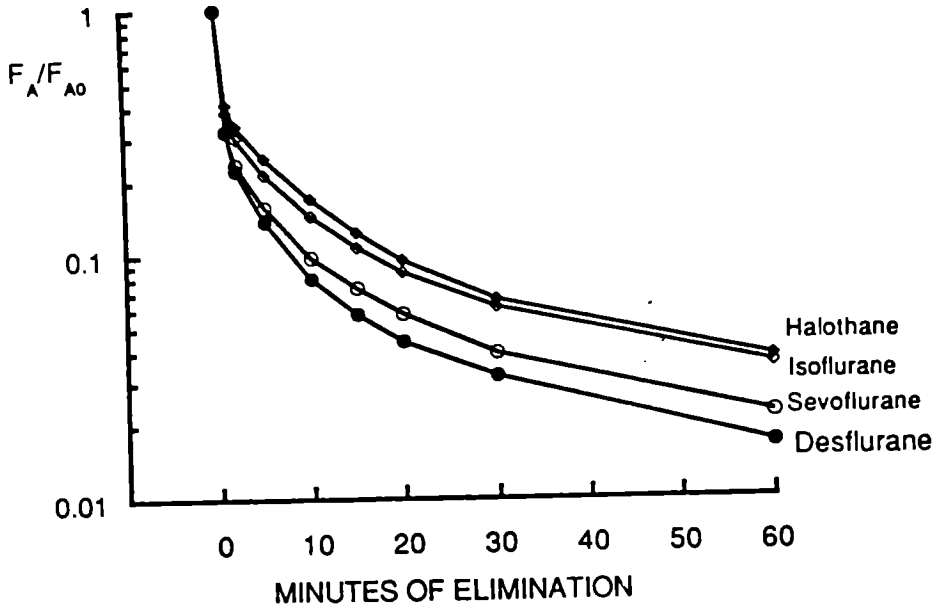


Fig. 13.15. The fall in alveolar concentration (F_A) relative to the alveolar concentration at the end of anesthesia (F_{AO}). Note that the newest, most insoluble volatile anesthetic, desflurane, is eliminated in humans more rapidly than are the other contemporary potent anesthetics. Not shown is information for methoxyflurane. If present, the curve for methoxyflurane would appear above that for halothane. From Eger,[326] with permission.

tissues (actual timing is influenced by agent solubility). Since the venous anesthetic pressure or tension equals that in the tissue within 10 or 15 min, about 75% of the blood returning to the lungs is the same as the alveolar tension. This presumes there has been no change in arterial anesthetic partial pressure during this time and thus uptake is reduced. Skin and muscle comprise the major bulk of the body (about 50% in humans) but at rest receive only about 15% to 20% of the CO, so saturation of these tissues requires several hours. Fat is a variable component of body bulk and receives only a small proportion of blood flow. Consequently, anesthetic saturation of this tissue is very slow because all anesthetics are considerably more soluble in fat than in other tissue groups (Table 13.2).

Other factors can influence the magnitude of the alveolar to arterial anesthetic partial pressure gradient. For example, abnormalities of ventilation-perfusion cause an alveolar-arterial gradient proportional to the degree of abnormality.[10,22,23] Others include loss of anesthetic via the skin[24–26] and into closed gas spaces[10,14,19] and metabolism.[10,14]

Overview

The rate with which the alveolar anesthetic concentration increases relative to the inspired concentration (i.e., the rate of change in anesthetic level) is often summarized as a plot of the ratio of F_A/F_I versus time. The position of individual curves representing different anesthetics on a plot is related to the solubility characteristics of the anesthetics (Fig. 13.13). The shape of the graph of F_A/F_I versus time is similar for all anesthetics (Fig. 13.13). A rapid initial rise results from the effect of alveolar ventilation bringing anesthetic into the lung. The rate of rise of the curve then decreases as uptake by the blood occurs. With time the highly perfused tissues of the body equilibrate with incoming blood so that eventually about three-quarters of the total blood flow returning to the heart has the same anesthetic partial pressure as it had when it left the lungs. Thus, further uptake from the lung is decreased, and the rate of approach of the F_A to F_I over time is further decreased.

Anesthetic Elimination

Recovery from inhalation anesthesia results from the elimination of anesthetic from the CNS. This requires a decrease in alveolar anesthetic partial pressure (concentration), which in turn fosters a decrease in arterial and then CNS anesthetic partial pressure (Fig. 13.9). Prominent factors accounting for recovery are the same as those for anesthetic induction. Therefore, factors such as alveolar ventilation, CO, and especially agent solubility greatly influence recovery from inhalation anesthesia. Indeed, the graphic curves representing the washout of anesthetic from alveoli versus time (Fig. 13.15) are essentially inverses of the wash-in curves. That is, the washout of the less soluble anesthetics is high at first (i.e., rapid washout by ventilation of the lung functional residual capacity) and then rapidly declines to a lower output level that continues to decrease but at a slower rate. The washout of more soluble agents is also high at first, but the magnitude of decrease in alveolar anesthetic concentration is less and decreases more gradually with time (Fig. 13.15).

An important factor during the washout period is the duration of anesthesia. This effect and a comparison of this effect between three agents spanning a range of blood solubilities is summarized in Fig. 13.16.[27] If a patient rebreathing anesthetic circuit (e.g., circle system) is in use and the patient is not disconnected from the circuit at the end of anesthesia, the circuit itself may also reduce the rate of recovery, just as the circuit was shown to decrease the rate of rise of anesthetic during induction. This influence of rebreathing circuits can be reduced by directing high flow rates of anesthetic-free O_2 into the anesthetic circuit (i.e., applying principles of a non-rebreathing circuit).

Other factors that are important to varying degrees to inhala-

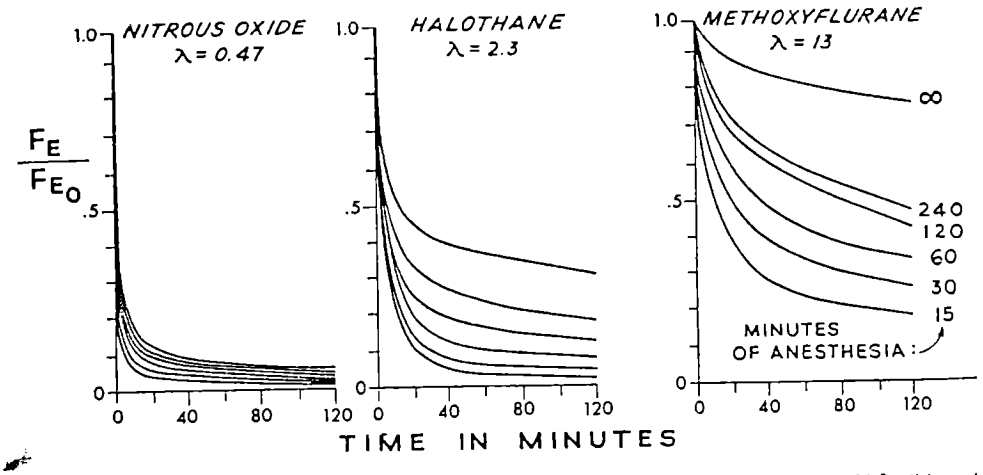


Fig. 13.16. The decrease in the alveolar anesthetic concentration (F_E) from the concentration at the time of breathing circuit disconnect (i.e., the beginning of recovery from anesthesia; F_{EO}) is influenced by both the solubility (λ) of anesthetic and the duration of anesthesia. From Stoelting and Eger,[27] with permission.

tion anesthetic elimination from the body include percutaneous loss, intertissue diffusion of agents, and metabolism. Transcutaneous movement of inhalation agent occurs, but the amount under consideration is small.[24–26,28] Intertissue diffusion is of theoretical interest, but its clinical importance is limited.[29–31] Metabolism may also play a small role with some inhalation anesthetics (e.g., methoxyflurane and perhaps even halothane), especially when associated with prolonged anesthesia.[29,32–34]

A special consideration associated with recovery after use of N_2O also deserves comment. *Diffusion hypoxia* is a possibility at the end of N_2O administration when the patient breathes air immediately rather than O_2 for at least a brief transition period (i.e., 5 to 10 min).[35–37] In this case a large volume of N_2O enters the lung from the blood. This early rapid inflow of N_2O to the lung displaces other gases within the lung. If at this time the patient is breathing air (only about 21% O_2) rather than 100% O_2, N_2O dilutes alveolar O_2, further reducing O_2 tension from levels found in ambient air. This action may cause life-threatening reductions in arterial oxygenation. Since the major effect is in the first few minutes after discontinuing N_2O, the condition can be prevented by administering pure O_2 at the conclusion of N_2O administration rather than allowing the patient to breathe ambient air immediately.

Biotransformation

Inhalation anesthetics are not chemically inert.[38] They undergo varying degrees of metabolism primarily in the liver but also to lesser degrees in the lung, kidney, and intestinal tract.[32,39–42] The importance of this is twofold. First, in a very limited way with older anesthetics, metabolism may facilitate anesthetic recovery. Second and more important is the potential for acute and chronic toxicities by intermediary or end metabolites of inhalation agents, especially on kidneys, liver, and reproductive organs.[32,42]

The magnitude of metabolism of inhalation anesthetic agents is determined by a variety of factors, including the chemical structure, hepatic enzyme activity (cytochrome P-450 enzymes located in the endoplasmic reticulum of the hepatocyte), the blood concentration of the anesthetic,[43] disease states, and genetic factors (i.e., some species and individuals are more active metabolizers of these drugs than are others, e.g., humans compared with rats).

Table 13.6. Biotransformation of inhalation anesthetics in humans

Anesthetic	% Anesthetic Metabolized	References
Methoxyflurane	50–75	34, 41
Halothane	20–46	34, 40, 329
Sevoflurane	2–5	53, 330
Enflurane	2–8	34, 331
Isoflurane	0.2	332
Desflurane	0.02	56
Nitrous oxide	0.004	293, 294

An indication of the extent of biotransformation of contemporary inhalation anesthetics is presented in Table 13.6. Sevoflurane degrades in vivo to about the same extent as isoflurane and as indicated by transient postanesthetic increases in blood and urinary fluoride levels in rats,[44–48] dogs,[47] horses,[49–51] swine,[52] and people.[53] The peak serum fluoride concentrations observed in people during and after sevoflurane anesthesia are low, and nephrotoxicity is not expected.[53,54] Desflurane resists degradation in vivo.[52,55,56] The increase in serum inorganic fluoride is much smaller than that found with isoflurane.[52,55,56]

For further information on the biotransformation of inhalation anesthetics in general and for specific details regarding individual anesthetic agents, readers are referred to reviews by Baden and Rice[32] and Mazze and Fujinaga.[42]

Anesthetic Dose: The Minimum Alveolar Concentration

In 1963 Merkel and Eger described what has become the standard index of anesthetic potency for inhalation anesthetics: the

minimum alveolar concentration (MAC).[57] The *MAC* is defined as the minimum alveolar concentration of an anesthetic at 1 atmosphere that produces immobility in 50% of subjects exposed to a supramaximal noxious stimulus. Thus, the MAC corresponds to the median effective dose (ED_{50}): Half of the subjects are anesthetized and half have not yet reached that "level." The dose that corresponds to the ED_{95} (95% of the individuals are anesthetized), at least in people, is 20% to 40% greater than the MAC.[58] Anesthetic potency of an inhaled anesthetic is inversely related to the MAC (i.e., potency = 1/MAC). From information presented earlier, it also follows that the MAC is inversely related to the oil-gas PC. Thus, a very potent anesthetic like the formally available agent methoxyflurane, which has a high oil-gas PC, has a lower MAC, whereas an agent with a low oil-gas PC has a higher MAC.

A number of characteristics of the MAC deserve emphasis.[10] First, the A in MAC represents *alveolar* concentration, not inspired or delivered (e.g., as from a vaporizer). This is important because the alveolar concentration is easily monitored with contemporary technology. Also, as we reviewed earlier, after sufficient time for equilibration (minutes), alveolar partial pressure will more closely approximate arterial and brain anesthetic partial pressures.

Second, the MAC is defined in terms of volume percent of 1 atmosphere and therefore represents an anesthetic partial pressure (P) at the anesthetic site of action; that is, remember, $P_x = (C/100) \cdot P_{bar}$, where P_x stands for the partial pressure of the anesthetic in the gas mixture, C is the anesthetic concentration in volume percent, and P_{bar} is the barometric or total pressure of the gas mixture. Thus, although the concentration at the MAC for a given agent may vary depending on ambient pressure conditions (e.g., sea level vs. high altitude), the anesthetic partial pressure always remains the same. For example, the MAC for isoflurane in healthy dogs is reported as 1.63 vol%. The study reporting this value was conducted at near sea level conditions at Davis, California (i.e., P_{bar} = 760 mm Hg). Based on the foregoing discussion, a MAC of 1.63 vol% represents an alveolar isoflurane partial pressure (P_{iso}) of 11.6 mm Hg. In comparison, for the same dog at Mexico City (elevation, 2240 m above sea level; P_{bar} = 584 mm Hg) the alveolar P_{iso} at the MAC is expected to be the same as determined at Davis (i.e., 11.6 mm Hg), whereas the MAC (i.e., the alveolar concentration) would be about 2.17 vol%.

Finally, it is important to note that the MAC is determined in healthy animals under laboratory conditions in the *absence* of other drugs and circumstances common to clinical use that may modify the requirements for anesthesia. General techniques for determining the MAC in animals are given elsewhere.[10,59–62] In determining the MAC in people the initial surgical skin incision has been the standard noxious stimulus used.[10] For the determination of the MAC in smaller animals (mice to dogs and pigs)[10,63,64] the standard stimulus has been application of a forceps or other surgical clamp to the base of the tail or the base of the dewclaw of the limb (e.g., pigs[62]), whereas electrical stimulus applied beneath the oral mucous membranes is most commonly used in larger species such as horses.[60]

The MAC values for contemporary inhalation anesthetics for a variety of animals commonly encountered in veterinary medicine are summarized in Table 13.7a and b. Values for humans are also listed for comparison. For values of agents of historical interest such as methoxyflurane, enflurane, or diethyl ether, readers are referred to the review in an earlier edition of this book or elsewhere.[10,64]

Since its original introduction, the MAC concept has been extended to other stimulus end points in an effort to better define and understand the anesthetic state. For example, Stoelting and coworkers[65] determined the value for the MAC of an anesthetic at which people opened their eyes on verbal command during emergence from anesthesia; this has been termed *MAC-awake*. The verbal stimulus is of course less intense than the surgical incision in people and thus the response occurs at a lower concentration of anesthetic than movement following incision. The end-tidal concentration preventing movement in response to tracheal intubation (the MAC for intubation) is more stimulating to people than is surgical incision and was described by Yakaitis and colleagues.[66,67] Roizen and colleagues[68] reported an even greater alveolar concentration necessary to prevent adrenergic response (rise in endogenous catecholamines) to skin incision (also in human patients) compared with the concentration necessary to just prevent movement; this is known as *MAC-BAR*. Thus, a group of response curves is possible and depends on the chosen strength of the stimulus applied.

In a single species the variability in the MAC (response to a noxious stimulus) is generally small and not substantially influenced by gender, duration of anesthesia, variation in arterial CO_2 partial pressure ($PaCO_2$) (from 10 to 90 mm Hg), metabolic alkalosis or acidosis, variation in arterial oxygen partial pressure (PaO_2) (from 40 to 500 mm Hg), moderate anemia, or moderate hypotension[10,64,69] (Table 13.8). Even between species the variability in the MAC for a given agent is usually not large. However, there is at least one notable exception (Table 13.7a). In humans, the MAC for N_2O is 104%, making it the least potent of the inhalation anesthetics currently used in this species. Its potency in other species is less than half that in humans (i.e., around 200%). Because the N_2O MAC is above 100% it cannot be used by itself at 1 atmosphere pressure in any species and still provide adequate amounts of O_2. Consequently, and assuming that the MAC values for combinations of inhaled anesthetics are additive, N_2O is usually administered with another more potent inhalant agent to thereby reduce the concentration of the second agent necessary for anesthesia (Fig. 13.17). However, because of the potency difference between animals and people, the amount of reduction differs in an important way. For example, administration of 60% N_2O with halothane reduces the amount of halothane needed to produce the MAC by about 55% in healthy people (Fig. 13.17) but reduces it only by about 20% to 30% in dogs. As noted in Fig. 13.17, the response of other animals most closely resembles that of dogs. Some physiological factors and drugs that influence the MAC are listed in Table 13.8.

Equipotent doses (i.e., equivalent concentrations of different anesthetics at the MAC) are useful for comparing effects of inhalation anesthetics on vital organs. In this regard anesthetic dose is commonly defined in terms of multiples of the MAC (i.e., 1.5

Table 13.7a. Minimum alveolar concentration values (%) for a variety of mammals at sea level or near sea level conditions

	Desflurane	Halothane	Isoflurane	Sevoflurane	N_2O
Cat	9.79[333] 10.27[334]	0.99[335,336] 1.14[337] 1.19[338]	1.28[339] 1.50[336] 1.61[338] 1.63[165] 1.90[334] 2.21[340]	2.58[341] 3.07[336] 3.41[334]	255[337]
Cow		0.76[342](calf)	1.14[343]		223[342] (calf)
Dog	7.2[344] 7.68–8.19[345] 10.3[346]	0.86[347] 0.87[337,348,349] 0.89[164,350] 0.92[351] 0.93[352] 1.01[356a]	1.28[165] 1.30[140] 1.31[353] 1.39[165] 1.39–1.50[354]	2.10[86] 2.36[350]	188[348] 222[337] 297[355]
Ferret			1.52[356] 1.74[357]		267[356]
Goat		1.29[358] 1.3[359]	1.2[71] 1.23[360] 1.29[358] 1.31[361] 1.43[362] 1.5[359]	2.33[358]	
Horse	7.02[363] 8.06[151]	0.88[60] 0.95[364] 1.02[365] 1.05[142]	1.31[60] 1.43[141] 1.44[366] 1.64[367]	2.31[368] 2.84[369]	205[213]
Monkey		0.89[337] 1.15[370]	1.28[370] 1.46[140]		200[337]
Mouse	6.6–9.1[a,371]	0.95[372] 1.00[373] 1.19–1.37[a,371] 1.59[374]	1.31–1.77[a,371] 1.35[372] 1.41[373]	2.7[375]	150[376] 275[373]
Pig	10.00[62]	0.90[377] 0.91[378] 1.25[379]	1.45[380] 1.48[377] 1.51[140] 1.55[381] 1.75[382] 2.04[62]	1.97[383] 2.12[377] 2.53[384] 2.66[92]	162[381] 195[382] 277[379]
Rabbit	8.90[344]	0.80[385] 0.82[386] 1.05[387] 1.39[388] 1.42[389] 1.44[390] 1.56[391]	2.05[388] 2.07[389] 2.12[390]	3.70[392]	

or 2.0 times the MAC or simply 1.5 MAC or 2.0 MAC). From the preceding discussion, therefore, the ED_{50} equals the MAC or 1.0 MAC and represents a light level of anesthesia (clearly inadequate in 50% of otherwise unmedicated, healthy animals). The ED_{95} is 1.2 to 1.4 MAC, and 2.0 MAC represents a deep level of anesthesia, in some cases even an anesthetic overdose. The concept of MAC multiples can be used to compare drug effects and contrast pharmacodynamics of multiple doses of a specific drug.

Pharmacodynamics: Actions and Toxicity of the Volatile Anesthetics

All contemporary inhalation anesthetic agents in one way or another influence vital organ function. Some actions are inevitable and accompany the use of all agents, whereas other actions are a special or prominent feature of one or a number of the agents. In addition, dose-response relationships of inhalation anesthetics are not necessarily parallel. Differences in action, and especially

Table 13.7a. Minimum alveolar concentration values (%) for a variety of mammals at sea level or near sea level conditions (*continued*)

	Desflurane	Halothane	Isoflurane	Sevoflurane	N_2O
Rat	5.72[393]	0.81[397]	1.17[397]	2.99[399]	136[407]
	6.48[394]	0.95[398]	1.28[405]	2.40[400]	155[408]
	6.85[395]	1.02[399]	1.30[406]	2.50[44]	204[172]
	7.10[396]	1.03[372]	1.38[401]		221[409]
		1.10[400]	1.46[372]		235[409]
		1.11[401]	1.46[395]		
		1.13[402,403]	1.58[357,398]		
		1.17[404]			
		1.23[395]			
Sheep		0.97[410]	1.58[410]		
Human (30–60 years)	6.00[411]	0.73[412]	1.15[416]	1.58[417]	104[423]
		0.74[413,414]		1.71[418]	
		0.77[415]		1.83[419]	
				1.84[420]	
				1.85[421]	
				1.9[422]	
				2.05[392]	

N_2O, nitrous oxide. Superscript numbers are reference numbers.
[a]Absolute value related to strain.

Table 13.7b. ED_{50} values for a variety of nonmammals[a]

	Desflurane	Halothane	Isoflurane	Sevoflurane	N_2O
Birds					
Chicken		0.85[61]			
Cockatoo			1.44[424]		
Crane			1.34[425]		
Duck		1.04[426]	1.30[427]		
Hawk			1.45[428]		220[428]
Parrot					
Amazon			1.47[424]		
African gray			1.91[424]		
Pigeon			1.51[428]		154[428]
Other					
Goldfish		0.76[429]			
Toad		0.67[430]			82.2[430]

ED_{50}, median effective dose; N_2O, nitrous oxide. Superscript numbers are reference numbers.
[a]Sea level or near sea level conditions.

undesirable action, of specific anesthetic agents form the basis for selecting one agent over another for a particular patient and/or procedure. Undesirable actions also provide primary impetus for development of new agents and/or anesthetic techniques.

Data from healthy animals exposed to equipotent alveolar concentrations of these drugs under controlled circumstances provide foundation information for this review. In other cases, results of studies of human volunteers form the basis of our understanding of some drug actions. Because animals are commonly allowed to breathe spontaneously during clinical management of general anesthesia (versus controlled mechanical ventilation) investigational results obtained from spontaneously breathing test animals are often considered baseline by veterinarians. In the broader anesthesiology and pharmacology literature, however, results of studies from human volunteers or animals administered precise amounts of inhalation anesthetics during controlled ventilation (and normocapnia) most commonly form the basis of comparison of pharmacodynamic differences. It is important to stress that many variables other than mode of ventila-

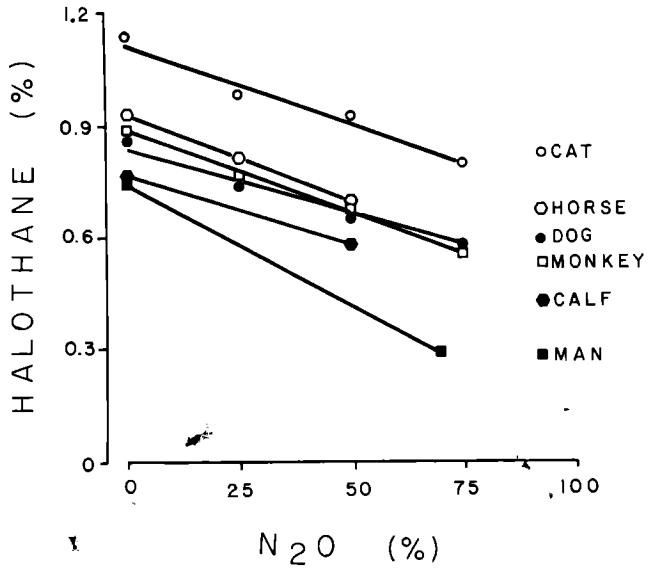


Fig. 13.17. When nitrous oxide (N_2O) is combined with halothane the alveolar concentration of halothane at minimum alveolar concentration is decreased. However, the halothane sparing imposed by nitrous oxide (N_2O) is less in animals compared with humans. From Steffey and Eger,[216] with permission.

tion commonly accompany anesthetic management of animals in both clinical and laboratory settings. These variables influence drug pharmacodynamics and may cause individuals to respond differently than test subjects that were studied under standardized conditions. Such confounding variables include species, duration of anesthesia, noxious (painful) stimulation, coexisting disease, concurrent medications, variation in body temperature, and extremes of age as examples.

Central Nervous System

Inhalation anesthetics affect the CNS in many ways. Mostly these agents are selected because they induce a reversible, dose-related state of CNS (somatic and motor), but also hemodynamic and endocrine, unresponsiveness to noxious stimulation: that is, a state of *general anesthesia*. Interestingly, although clinical anesthesia was introduced more than 150 years ago, the sites and mechanisms by which general anesthetics (including the inhalation anesthetics) cause unresponsiveness to surgical or other forms of noxious stimulation remain unknown. Traditionally, this summary state we refer to as general anesthesia was assumed to result from a focus in the brain. However, mounting evidence is causing a shift in thinking such that this state we know as general anesthesia is likely the collection of a number of end points that are distinct and site specific, and include supraspinal and spinal events. For example, actions focused in the brain (especially the cerebral cortex and thalamus) mediate such centrally recognized components of general anesthesia as amnesia (at least in humans) and hypnosis (sleep), whereas the spinal cord appears to be a critical site of anesthetic action that suppresses noxious-evoked movement.[70–72] In-depth review of known neural effects and theories of mechanism of action of inhalation anesthetics is beyond the scope of this clinically focused review. Accordingly, readers with further interest in these subjects are referred to recent reviews by investigators currently active in this work.[73,74]

Inhalation anesthetics influence electrical activity of the brain, cerebral metabolism, cerebral perfusion, intracranial pressure, and analgesia—issues of critical importance to anesthetic management of animals.

Electroencephalographic Effects

The electroencephalograph (EEG) is used to help identify pathological brain disorders and to predict the outcome of brain insults. Studies have also shown that general anesthesia alters EEG parameters, and we apply this knowledge to better understand anesthetic circumstances. The EEG signal (wave) contains two basic parameters within a time frame (i.e., continues or an epoch): amplitude and frequency. *Amplitude* is the electrical height of the waves in volts, and *frequency* is the number of times per second the wave crosses the zero voltage reference point. The signal from an alert, attentive brain is usually low amplitude and high frequency. When events that lead the brain to produce higher frequencies occur, the EEG is described as *activated*, and it is considered *depressed* when slower frequencies are noted. General characteristics of the normal EEG are that it is symmetrical, the patterns are predictable, and spike waveforms are not present. All anesthetics do not produce exactly the same changes in EEG pattern as dose (anesthetic depth) increases, so the generic correlation of the raw EEG pattern with anesthetic dose is not precise. Indeed, despite some weak correlations and its usefulness as an indication of changing anesthetic depth, no parameter has had sensitivity and specificity sufficient to justify use of the EEG alone as a reliable index of anesthetic depth.[75] With technological advances of recent years, research has focused on use of processed EEG parameters (e.g., the bispectral index) as improved descriptions of anesthetic states. However, this subject is beyond the scope of this chapter and therefore is explored elsewhere (see Chapter 38).

In general, as the depth of anesthesia increases from awake states, the electrical activity of the cerebral cortex becomes desynchronized. Using isoflurane as an example of the general EEG response to volatile anesthetics,[1] the frequency of the EEG activity (alveolar concentrations of <0.4 MAC) initially increases. With further increases in anesthetic concentration, a decrease in frequency and increased amplitude of the EEG waves occur. The wave amplitude increases to a peak (about 1 MAC), and then, with further dose increase, the amplitude progressively declines (burst suppression occurs at about 1.5 MAC; i.e., bursts of slow high-voltage activity separated by electrical silence) and eventually becomes flatline (predominance of electrical silence). With isoflurane, an isoelectric pattern occurs at about 2.0 MAC, whereas, on the other extreme, it is not seen with halothane until >3.5 MAC. Electrical silence does not occur with enflurane. The two newest volatile anesthetics—sevoflurane and desflurane—cause dose-related changes similar to those of isoflurane.[76–78]

Several anesthetics in contemporary use have epileptogenic potential, especially in individuals predisposed to seizures. Enflurane is most prominent in this regard among the inhalation

Table 13.8. Some factors that influence the value of the minimum alveolar concentration (anesthetic requirement)

No Change	Increase	Decrease
Arterial blood pressure >50 mm Hg[431]	Drugs causing CNS stimulation	Drugs causing CNS depression[a]
Atropine, glycopyrrolate, and scopolamine[335]	Amphetamine	Other inhaled anesthetic
Duration of anesthesia	Ephedrine	Nitrous oxide[19]
Gender	Morphine (horse[141])	Injectable anesthetics
Hyperkalemia and hypokalemia	Laudanosine[391]	Ketamine[243]
Metabolic acid-base change	Physostigmine[432]	Lidocaine[340,352]
PaO_2 > 40 mm Hg	Hyperthermia (to 42°C)	Thiopental[433]
$PaCO_2$ = 15–95 mm Hg		Preanesthetic medication
		Acepromazine[434–436]
		Diazepam[437–439]
		Detomidine[366]
		Fentanyl[440]
		Medetomidine[441,442]
		Meperidine[241]
		Midazolam[443]
		Morphine[444]
		Xylazine[367]
		Other
		Adenosine
		Central anticholinergic[432]
		5-HT antagonist[445]
		Arterial blood pressure < 50 mm Hg
		Hyponatremia
		Hypothermia
		Increasing adult age
		PaO_2 < 40 mm Hg
		$PaCO_2$ > 95 mm Hg
		Pregnancy

5-HT, 5-hydroxytryptophan; CNS, central nervous system; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure. Superscript numbers are reference numbers.

[a]List of example drugs are intended to be representative, not exhaustive. The list is summarized from previous reviews[10,59,64] except where indicated by superscript reference numbers.

anesthetics. Seizure activity is of concern because neuronal injury may result if demands for substrate (especially O_2) for maintaining neuronal function are greater than supply. A second concern is trauma to patients experiencing tonic-clonic muscle twitching, especially among horses. People assisting in the anesthetic and surgical management of these large patients may become injured. Finally, there is concern that seizures may persist into the postanesthetic period, especially unpredictably and when they occur in less well-controlled circumstances.

Systematic studies of EEG activity in people[79] and dogs[80] showed that enflurane was associated with spontaneous or noise-initiated intensified seizures. In addition, enflurane induces seizure activity that is associated with substantial increases in cerebral blood flow and cerebral metabolic use of O_2. In the studies by Joas et al.,[80] halothane, methoxyflurane, and isoflurane did not cause the frank epileptoid activity in dogs that was induced by enflurane. Indeed, both halothane and isoflurane have the capacity to produce an isoelectric EEG, with isoflurane doing so at a lower dose.[1] Present wide-spread opinion is that epileptogenesis is not a clinical concern with either agent.

The EEG responses to the two newest anesthetics—desflurane and sevoflurane—are reportedly similar to those of isoflurane,[76–78] and all three can suppress drug-induced convulsive behavior.[81–85] However, there are reports of seizure activity in animals[86,87] and human patients[88,89] during sevoflurane anesthesia. Because of the EEG-activating property of enflurane and perhaps sevoflurane it seems prudent to avoid their use in situations when events might predispose patients to seizures and when reasonable anesthetic alternatives exist.

Cerebral Metabolism

All volatile anesthetics decrease cerebral metabolic rate (CMR; cerebral O_2 consumption). The magnitude of decrease is least with halothane but similar with isoflurane, sevoflurane, and desflurane.[76,81,86,90,91]

Cerebral Blood Flow

The volatile anesthetics cause no change or often an increase in cerebral blood flow (CBF).[76,81,86,91,92] The effect on CBF is likely the sum of a tendency both to decrease as a result of anes-

thesia reducing cerebral O_2 consumption and increase due to vasodilation caused by direct anesthetic action on vascular smooth muscle.[93] This can be summarized by saying the ratio of CBF relative to CMR is increased by the potent inhalation anesthetics. The effect is anesthetic dose related and influenced by agent. The rank order of CBF increase is generally regarded as halothane > enflurane, isoflurane, desflurane, and sevoflurane (all four being similar).[69] Effects on CBF have been shown to be time dependent in animals[94–96] but not in humans.[97]

Intracranial Pressure

The inhalation anesthetics increase intracranial pressure (ICP), and this change parallels the CBF increase that similarly accompanies these agents.[76,98] In larger animals such as horses, body and head position further impacts the heart-to-brain hydrostatic gradient, which in turn can further impact ICP. Consequently, body position necessitates even greater consideration in anesthetized horses than is commonly considered in smaller species so as to minimize risks of inadequate CBF and cerebral ischemia.[99] It is generally regarded across species lines that ICP increases can be decreased by hyperventilation and decreasing $PaCO_2$.[100] Accordingly, use of hyperventilation is a common strategy in clinical situations in which even small elevations in ICP are of special concern. Mechanical ventilation and accompanying reduced $PaCO_2$ also reduce ICP in horses.[101] However, because of the commonly associated, often large decrease in systemic blood pressure in this species, cerebral perfusion pressure may decrease out of proportion and further reduce CBF.

Analgesia

A clinically desirable general anesthetic includes both hypnotic and analgesic actions. However, studies to differentiate hypnotic potency from analgesic potency within the anesthetic-concentration range is, at the least, difficult to interpret. Studies of subanesthetic concentrations of inhalation anesthetics have been preformed but with conflicting results. Some inhalation anesthetics have been reported to increase the response threshold to noxious stimulation compared with like, but unmedicated, conditions (e.g., diethyl ether), whereas others (e.g., isoflurane and sevoflurane) do not change the threshold,[102,103] and still others, like halothane,[104] may decrease the threshold for response and contribute a heightened awareness to noxious stimulation (i.e., antianalgesia). More recent work even suggests that inhalation anesthetics (including diethyl ether and N_2O) can be antianalgesic.[105] An antianalgesic effect may enhance perception of noxious stimulation (pain) for varying periods during, for example, recovery from anesthesia when low-level alveolar concentrations are reached.

Respiratory System

Inhalation anesthetics depress respiratory system function. The volatile agents, in particular, decrease ventilation in a drug-specific and species-specific manner. Depending on conditions, including species of interest, some of the most commonly considered measures of breathing effectiveness—that is, breathing rate and depth (tidal volume)—may not be revealing or may even be misleading. In general, spontaneous ventilation progressively decreases as inhalation anesthetic dose is increased, because at low-dose tidal volume decreases more than frequency increases. As anesthetic dose is further increased, respiratory frequency also decreases. In otherwise unmedicated animals (as well as people) anesthetized with volatile agents, respiratory arrest occurs at 1.5 to 3.0 MAC (Table 13.9). The overall decrease in minute ventilation and the likely variable increase in dead-space ventilation (causing an increase in the dead space to tidal volume ratio, V_D/V_t, from a normal of about 0.3 to 0.5 or more) reduce alveolar ventilation. Decreases in alveolar ventilation are out of proportion to decreases in CO_2 production (O_2 use is decreased by general anesthesia), such that $PaCO_2$ increases (Fig. 13.18). In addition, the normal stimulation to ventilation caused by increased $PaCO_2$ (or decreased PaO_2) is depressed by the inhalation anesthetics, presumably via the action of these agents directly on the medullary and peripheral (aortic and carotid body) chemoreceptors.[106–109] Changes in perianesthetic PaO_2 other than what might be related to the magnitude of alveolar ventilation are not notably different among the various inhalation anesthetics in a given species.

Table 13.9. Apneic index (AI) in various species

	Desflurane		Halothane		Isoflurane	
	MAC	AI	MAC	AI	MAC	AI
Cat					1.63	2.4[165]
Dog	7.2	2.4[119]	0.87	2.9[349]	1.28	2.5[165]
Horse			0.88	2.6[60]	1.31	2.3[60]
Pig	9.8	1.6[119,446]				
Rat			1.11	2.3[173]	1.38	3.1[172]
Human	7.25	1.8[121]	0.77	2.3[121]	1.15	1.7[121]

Minimum alveolar concentration (MAC) is given in volume percent, and the AI is a ratio of the end-tidal anesthetic concentration at apnea and MAC. Similar data are not currently available for sevoflurane.

Bronchospasm is associated with some diseases and other patient conditions and contributes to increased airway resistance. A variety of early studies indicated that, among anesthetics available at the time, halothane was the most effective bronchodilator.[110,111] The effect is believed to result at least partially by decreasing cholinergic neurotransmission.[112,113] For years, therefore, it has been the anesthetic agent of choice for patients at risk of bronchospasm. The work of Hirshman and colleagues[114,115] suggests that isoflurane and perhaps enflurane were as effective in decreasing experimentally produced airway resistance and therefore were good alternatives to halothane. More recent work with isoflurane, sevoflurane, and desflurane indicates that relaxation of constricted bronchial muscles by these agents is at least equal to or exceeds that caused by halothane.[113,116,117]

Avoidance of airway irritation by inspiring inhalation anes-

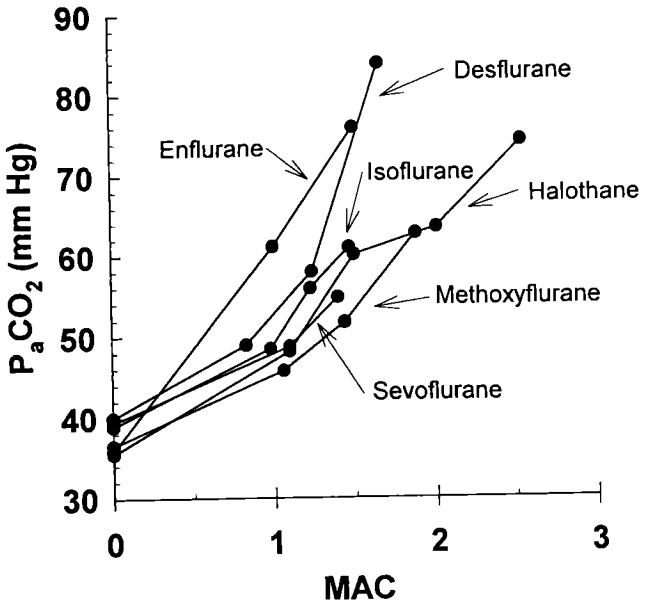


Fig. 13.18. Respiratory response to an increase in the alveolar concentration (expressed in as a multiple of the minimum alveolar concentration [MAC]) of inhalation anesthetics in humans. $PaCO_2$, arterial carbon dioxide partial pressure. Data are taken from multiple sources.[107,121–125]

thetics is important especially during induction of anesthesia because the irritation may cause breath holding, coughing, and laryngospasm (particularly in some species such as primates [human and nonhuman]) that, in turn, result in arterial oxyhemoglobin desaturation. At least in humans, none of the potent inhalation anesthetics seem to have irritant properties at subanesthetic concentrations. However, patient objection and airway irritation is evident with desflurane (and to a lesser degree with isoflurane[118]) at concentrations of 7% or greater,[119,120] and as a result desflurane is not commonly used for anesthetic induction in human patients. Airway irritation has not been a generally recognized problem associated with induction of anesthesia in animals commonly anesthetized by veterinarians.

Arterial Carbon Dioxide Tension

The $PaCO_2$ is the most frequently used index of respiratory system response to general anesthetics. All contemporary inhalation anesthetics depress alveolar ventilation and, as a consequence, increase $PaCO_2$ in dose-related fashion. Figure 13.18 summarizes the effects of inhalation anesthetics in humans, the species for which data are most complete.[107,121–125] Actual rank order of the magnitude of hypoventilation imposed by the four contemporary volatile anesthetics at a common alveolar dose differs slightly depending on the species.

Factors Influencing Respiratory Effects

Mode of Ventilation Ventilation is often assisted or controlled during inhalation anesthesia to compensate for the anesthetic-induced respiratory depression. Controlled mechanical ventilation (i.e., the anesthetist controls both respiratory frequency and tidal volume) is used to predictably maintain a normal, or some other specific, $PaCO_2$ during anesthesia. Assisted ventilation (i.e., the anesthetist augments tidal volume, but the animal determines its own breathing frequency) is used to attempt to improve the efficiency of oxygenating arterial blood and reduce the work of breathing but is usually not effective in substantially lowering $PaCO_2$ compared with circumstances associated with spontaneous ventilation (i.e., the animal controls both the rate and depth of breathing).[126,127]

Duration of Anesthesia Respiratory function, including $PaCO_2$, is little changed for as long as up to 10 h of constant, low-dose halothane (or methoxyflurane) in dogs.[128,129] This is also supported by work in humans[130] anesthetized with constant low-dose halothane. However, in horses anesthetized for 5 h with a constant dose of 1.2 MAC isoflurane a substantial temporal increase in $PaCO_2$ was noted.[131] A similar, but more modest, trend was noted in horses when halothane was used for anesthesia.[132,133] At least in some species, if alveolar dose of halothane is increased above about 1.0 to 1.3 MAC and maintained constant at a heightened level, the magnitude of change in hypoventilation also worsens with time.[129] Conversely, there is evidence for recovery from the ventilatory depressant effects of volatile anesthetics in humans.[125]

Surgery and Other Noxious Stimulation Noxious stimulation may cause sufficient central nervous stimulation to lessen the ventilatory depression of the inhalation anesthetic.[134–137] This effect is of course diminished with increasing anesthetic depth.

Concurrent Drug Administration In humans the substitution of N_2O for an equivalent amount of a concurrently administered, more potent volatile agent such as isoflurane lowers $PaCO_2$ more (prevents hypoventilation) than does the volatile agent alone.[19] In dogs and monkeys anesthetized with halothane, ventilation was at least as, and sometimes more, depressed when N_2O was substituted for a portion of the halothane requirement.[138,139] The addition of opioid drugs like morphine may increase the respiratory depression produced by an inhalation anesthetic.[136,140–142]

Cardiovascular System

All of the volatile inhalation anesthetics cause dose-dependent and drug-specific changes in cardiovascular performance. The magnitude and sometimes direction of change may be influenced by other variables that often accompany general anesthesia (Table 13.10). The mechanisms of cardiovascular effects are diverse but often include direct myocardial depression and a decrease in sympathoadrenal activity.

Cardiac Output

All of the volatile anesthetics decrease CO. The magnitude of change is dose related and depends on agent. In general, among the contemporary agents in use with animals, halothane depresses CO the most.[1,143–145] Desflurane in many ways is similar in cardiovascular action to isoflurane, whereas sevoflurane has

Table 13.10. Factors that influence cardiovascular effects of inhalation anesthetics

Anesthetic dose
Duration of anesthesia
Concurrent drug therapy
Intravenous fluid therapy
Magnitude of $PaCO_2$
Mechanical ventilation
Noxious stimulation

$PaCO_2$, arterial carbon dioxide partial pressure.

characteristics resembling both halothane and isoflurane. All three of the newer volatile anesthetics tend to preserve CO at clinically useful concentrations.[51,119,146–154] The decrease in CO is largely due to a decrease in stroke volume as a result of dose-related depression in myocardial contractility.[1,119,150,155–157]

The effect of inhalation anesthetics on heart rate (HR) is variable and depends on agent and species. For example, in humans, HR is not substantially altered with halothane anesthesia but is usually increased by isoflurane, desflurane, and sevoflurane.[153,158,159] Compared with conditions in awake, calm dogs, HR is increased with the use of any of the four anesthetics listed.[149,154] There is evidence to suggest that differences between agents in the degree of increase in HR in dogs are explained by differences in the vagolytic activity of the agents.[152] In dogs the HR usually remains constant over a range of clinically useful alveolar concentrations in the absence of other modifying factors (e.g., noxious stimulation).[143,144,149,154,160,161] The distribution of blood flow to organs is altered during inhalation anesthesia. Readers with special interest in these changes are referred elsewhere for further information.[162,163]

Arterial Blood Pressure

Volatile anesthetics cause a dose-dependent decrease in arterial blood pressure (Fig. 13.19).[15,51,143,147,151,154,164–168] In general the dose-related decrease in arterial blood pressure is similar regardless of the species studied.[60,143,145,148,164–166,168–170] In animals the dose-related decrease in blood pressure with all four of the contemporary agents is usually related mostly to a decrease in stroke volume. In some cases (agent and/or species) a decrease in peripheral vascular resistance may also play an important, but lesser, role. This common scenario in animals differs from results generally reported from studies with people anesthetized at least with isoflurane, sevoflurane, and desflurane, whereby pressure decreases primarily from a decrease in systemic vascular resistance.[15,171] Indices of anesthetic influence on cardiovascular collapse are listed in Table 13.11.[143,172,173]

Cardiac Rhythm and Catecholamines

Inhalation anesthetics may increase the automaticity of the myocardium and the likelihood of propagated impulses from ectopic sites, especially from within the ventricle.[174] Although spontaneously derived dysrhythmias were most notable with earlier inhalation anesthetics (e.g., halothane), none of the three most recently introduced ether-derivative agents appear to predispose the heart to generated extrasystoles. However, any such effect can be exaggerated by adrenergic agonists.[175] The association of cardiac dysrhythmias with adrenergic drugs and anesthetic agents has received extensive study.

Inhalation anesthetics may sensitize the heart to arrhythmogenic effects of catecholamines. Halothane is most notable in this regard, as it markedly reduces the amount of epinephrine necessary to cause ventricular premature contractions.[176] There is some evidence that deeper levels of halothane decrease this incidence,[177–179] but this is not a consistent finding.[180] Enflurane and methoxyflurane are less potent in regard to their ability to sensi-

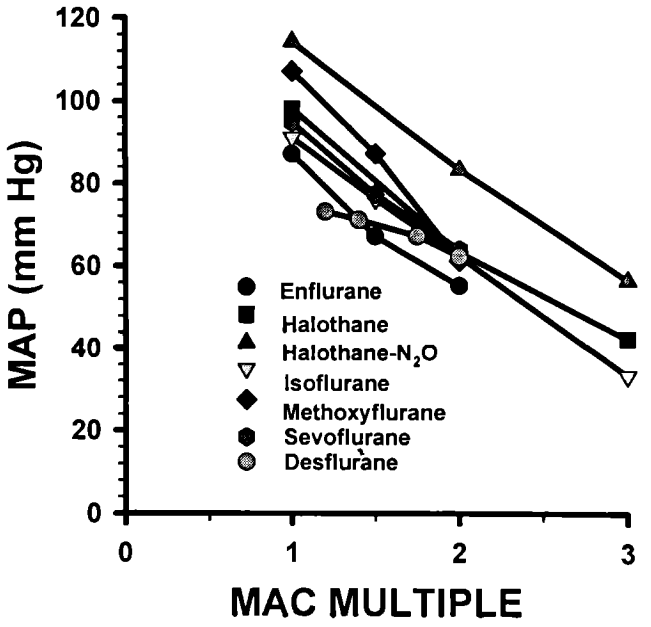


Fig. 13.19. Inhalation anesthetics cause a dose (expressed as multiples of the minimum alveolar concentration [MAC])-dependent decrease in mean arterial blood pressure (MAP) in dogs whose ventilation is mechanically controlled to produce eucapnia. N_2O, nitrous oxide. Data are from many sources and referenced in the text.

Table 13.11. Anesthetic-induced cardiovascular depression as expressed by cardiovascular anesthetic indices

Desflurane	Halothane	Isoflurane
Dog[a]	2.84	2.69
Pig[b]	2.45	3.02
Rat[c]	3.0	5.7

[a]The anesthetic concentration causing death in ventilated dogs related to the minimum alveolar concentration (MAC).[119]
[b]Mean fatal dose related to the MAC.[446]
[c]Heart concentration of anesthetic at cardiovascular failure related to heart concentration of anesthetic at establishment of anesthesia.[172,173]

tize the heart to arrhythmogenic effects of epinephrine, and isoflurane, desflurane, and sevoflurane are least arrhythmogenic.[1,179,181–186] The potential for dysrhythmias follows administration of most catecholamine-type drugs, although the magnitude of such potential varies with the drug coadministered[186–191] and other associated conditions.[192] Such considerations are important in the design of anesthetic plans for patients in which it is desirable or necessary to administer catecholamines, for example, local application to minimize blood oozing from highly vascular surgical sites, to minimize blood pressure, or for CO support, or in patients in which high blood levels of endogenous catecholamines are anticipated.

Factors Influencing Circulatory Effects

A variety of circumstances occasionally associated with the anesthetic management of veterinary patients may add to or negate the primary effects of the anesthetic. In most cases the most profound modifications of drug action are on cardiovascular function. Some factors influencing cardiovascular performance include mechanical ventilation and alterations in $PaCO_2$, noxious (surgical) stimulation, duration of anesthesia, and coexisting drugs.

Mode of Ventilation and $PaCO_2$ There may be considerable difference in the cardiovascular effects of inhalation anesthetics in animals breathing spontaneously compared with when their breathing is mechanically controlled (e.g., intermittent positive-pressure ventilation [IPPV]) to produce and maintain a normal $PaCO_2$. In general, and considering a broad range of circumstances, cardiovascular function is usually depressed during IPPV relative to actions during spontaneous ventilation. Such action results from either the direct mechanical actions (e.g., intermittent elevation of intrathoracic pressure and resultant decrease in venous return to the heart) or lessening of the indirect pharmacological action of $PaCO_2$[193] or both. Carbon dioxide has pharmacological actions important for these considerations. For example, an increased $PaCO_2$ has direct depressant actions on the heart and smooth muscle of the peripheral blood vessels (i.e., vessel dilation) but indirect (via sympathetic nervous system) stimulation of circulatory function.

In generally healthy, sympathetically intact animals (light anesthesia) the stimulatory actions of hypercapnia usually predominate, so increased CO and arterial blood pressure usually accompany an increase in $PaCO_2$, becoming lower when $PaCO_2$ is normalized.[51,126,145,151,164,168,169,194–197]

Noxious Stimulation Noxious stimulation during anesthesia modifies the circulatory effect of inhalation anesthetics via stimulation of the sympathetic nervous system. An increase in arterial blood pressure and HR (CO) commonly accompanies noxious stimulation.[68,136,137,198,199] The response is anesthetic dose related. For example, Roizen et al.[68] and Yasuda et al.[198] showed that deeper levels of halothane and enflurane decreased or prevented surgically induced increases in serum norepinephrine levels in human patients.[68] Anesthetic doses that block the response are in the range of 1.5 to 2.0 MAC.

Duration of Anesthesia Some cardiovascular effects of inhalation anesthetics may change with duration of anesthesia. For example, in humans, halothane anesthesia lasting 5 to 6 h is associated with an increase in values of some measures of cardiovascular function, such as CO and HR.[195,200] Similarly, varying degrees of time-related changes have been reported with the use of enflurane,[125] desflurane,[159,201,202] and others.[158,201–205]

Temporal changes in cardiovascular function have also been reported in a variety of animals with the use of halothane,[129,132,206,207] isoflurane,[131,206,208] and sevoflurane.[208] Dose of anesthetic[129,158,209] and body posture during anesthesia[133,210] apparently also play a temporal role in some species.

The causes of these changes remain unclear. In vitro, depression of the cat papillary muscle exposed to a constant concentration of halothane does not vary over a 3-h period.[211] This observation suggests that temporal effects associated with inhalation anesthetics are not the result of improved intrinsic cardiac function. Studies on human volunteers have shown that temporal responses to halothane can be prevented if the subjects are given propranolol before anesthesia, which suggests that the mechanism is related to increasing sympathetic nervous system activity.[212]

Usually the temporal changes associated with inhalation anesthetics are of only minor or no concern to clinicians. However, such changes must be considered when interpreting results of laboratory studies in which these agents are used for anesthetic management.

Concurrent Drug Administration Drugs administered immediately before or in conjunction with inhalation anesthetics (preanesthetic medication, injectable anesthetic induction drugs, vasoactive and cardiotonic drugs, etc.) may influence cardiovascular function by altering the anesthetic requirement (i.e., the MAC and thereby increase or decrease anesthetic level) or by their own direct action on cardiovascular performance.

For example, N_2O is used on occasion as a substitute for a portion of a more potent inhalation anesthetic. Because of its own anesthetic potency (albeit small; remember, the MAC for N_2O in animals is in the range of 2 atmospheres [Table 13.7]) its use may facilitate delivery of a reduced amount of the potent volatile agent and thereby contribute to some cardiovascular sparing. Nitrous oxide may depress the myocardium directly, but this effect is usually counterbalanced by its sympathomimetic effect, often resulting in a net improvement in cardiovascular function compared with conditions without N_2O. In animal patients the magnitude of N_2O effect is clinically limited and species dependent.[138,139,166,213,214] More complete summaries of its cardiovascular actions have been published elsewhere.[215,216]

Injectable drugs, such as acepromazine, α_2-agonists, thiobarbiturates, and dissociatives (e.g., ketamine), are frequently administered to animals as part of their anesthetic management. These drugs confound the primary effects of the inhalation anesthetics and may accentuate cardiovascular depression. On the other hand, sympathomimetic drugs, such as ephedrine,[217] dopamine, and dobutamine,[218,219] are frequently given to counteract unwanted cardiovascular depression of the anesthetic.

Effects on the Kidneys

It is generally regarded that present-day volatile inhalation anesthetics produce similar mild, reversible, dose-related decreases in renal blood flow and glomerular filtration rate and that such changes largely reflect an anesthetic-induced decrease in CO.[171] However, some studies show little or no change in these kidney-related parameters.[44,163,220,221]

As a consequence of the anesthetic-induced decrease in glomerular filtration, healthy anesthetized animals commonly produce a smaller volume of concentrated urine compared with when awake. An increase in serum urea nitrogen, creatinine, and inorganic phosphate may accompany especially prolonged anesthesia.[222–225] The reduction in renal function is highly influenced by an animal's state of hydration and hemodynamics during anesthesia.[226] Accordingly, attendant intravenous fluid therapy and prevention of a marked reduction in renal blood flow will lessen or counteract the tendency for reduced renal function. In most cases, effects of inhalation anesthesia on renal function are rapidly reversed after anesthesia.

Among the inhalation anesthetics, methoxyflurane is the most nephrotoxic. Although it is no longer available for use in human or animal patients, its actions are of pathophysiological interest and therefore is briefly reviewed here. Particularly in humans and some strains of rats, the use of methoxyflurane caused renal failure that was characterized not by oliguria but by a large urine volume unresponsive to vasopressin.[32] This was caused by the biotransformation of methoxyflurane and the large release of free fluoride ion that, in turn, directly damaged the renal tubules. Although renal injury in animals is rare, renal injury has been reported in dogs when methoxyflurane was used in combination with tetracycline antibiotics[227] and flunixin.[227]

With the possible exception of enflurane and sevoflurane, the breakdown of other inhalation anesthetics does not pose a risk of fluoride-induced nephrotoxicity. Biotransformation of enflurane and sevoflurane by humans following a moderate duration of anesthesia causes serum inorganic fluoride concentrations to increase even beyond the 50-μmol/L level, which is normally considered the nephrotoxic threshold in humans.[32,171,228,229] However, clinical, histological, or biochemical evidence of injury related to increases in fluoride has only rarely been reported in human patients. The overriding consensus is that sevoflurane has little potential for nephrotoxicity caused by defluorination.[32,171] Two factors may explain the general lack of injury despite the body's ability to degrade sevoflurane. In 1977, Mazze et al.[230] proposed that the area under the serum fluoride concentration-versus-time curve may be a more important determinant of nephrotoxicity than is peak serum fluoride concentration. Because sevoflurane is poorly soluble and is rapidly eliminated via the lungs the duration of its availability for biotransformation is notably limited. More recently, Kharasch and coworkers[231] proposed another consideration: Sevoflurane is primarily metabolized by the liver, whereas hepatic and renal sites are important for methoxyflurane breakdown. The relative lack of intrarenal anesthetic defluorination may markedly reduce its nephrotoxic potential. Studies have confirmed the increase in serum fluoride in horses anesthetized with sevoflurane.[49–51] In these reports the magnitude and time course of fluoride increase were similar to that reported for humans. In addition, as with humans, no evidence has been reported of untoward renal effects associated with the increase in fluoride in horses.

Sevoflurane is degraded by CO_2 absorbents such as soda lime and Baralyme.[45,53] A nephrotoxic breakdown product—compound A—is produced.[45,232] Compound A can cause renal injury and death in rats,[233] and the concentration threshold for nephrotoxicity in rats[234–236] is within the range of concentrations that may be found associated with the anesthetic management of human patients.[237] Not surprisingly, compound A is formed in the breathing circuits used for animals in veterinary medical practice.[238] The ultimate importance of in vitro sevoflurane degradation to the well-being of veterinary patients like dogs, cats, and horses[50] remains to be established. Until such time that additional data appear, it seems prudent to avoid sevoflurane for prolonged anesthesia especially with concurrent low fresh gas inflow to the breathing circuit (which promotes the concentration of compound A) and in patients with known or marginal kidney disease.

Effects on the Liver

Depression of hepatic function and hepatocellular damage may be caused by the action of volatile anesthetics. Effects may be mild and transient or permanent, and injury may be by direct or indirect action. Studies by Reilly et al.[239] suggested that at least halothane (but likely also other potent inhalation anesthetics) substantially inhibits the drug-metabolizing capacity of the liver. A reduction in intrinsic hepatic clearance of drugs along with anesthetic-induced alteration of other pharmacokinetically important variables (e.g., reduced hepatic blood flow) fosters a delayed drug removal or an increase in plasma drug concentration during anesthesia. Examples of such circumstances have been reported.[239–243] Prolonged or increased (relative to conditions in the unanesthetized animal) plasma concentrations of some drugs have important toxic implications, especially in physiologically comprised patients.

All of the potent inhalation anesthetics can cause hepatocellular injury by reducing liver blood flow and oxygen delivery. However, available data suggest that, of the four contemporary volatile anesthetics, isoflurane is most likely to better maintain tissue O_2 supply and thereby is the agent least likely to produce liver injury even when administered for prolonged periods. The effects of the two newest agents sevoflurane and desflurane are nearly similar to isoflurane, whereas halothane produces the most striking adverse changes.[32,147,163,167,244–250] Results of investigations indicate that ancillary influences, including the use of N_2O,[251] concurrent hypoxia,[249,252–254] prior induction of hepatic drug-metabolizing enzymes,[255,256] mode of ventilation,[257] and positive end-expired pressure,[258] may worsen conditions and increase the likelihood of hepatocellular damage.

It now appears that especially halothane produces two types of hepatotoxicity in susceptible individuals. One is a mild, self-limiting postanesthetic form of hepatocellular destruction and associated increase in serum concentrations of liver enzymes. Signs of hepatotoxicity occur shortly after anesthetic exposure. The other

is a rare, severe, often fatal hepatotoxicity with delayed onset and largely clinically limited to human patients (i.e., halothane hepatitis) and thought to be an immune-mediated toxicity.[259,260] The mechanism of halothane hepatitis may also be family related.[261] The increased incidence of hepatic injury associated with halothane was the principal factor leading to the decrease in the use of halothane for human patients nearly three decades ago.

Effects on Skeletal Muscle: Malignant Hyperthermia

Malignant hyperthermia (MH) is a potentially life-threatening pharmacogenetic myopathy that is most commonly reported in susceptible human patients[262,263] and swine[264] (e.g., Landrace, Pietrain, or Poland China strains). However, reports of its occurrence in other species are available.[265–271] Its clinicopathological, histopathological, and genetic basis has recently been further described for horses.[272,273] All of the four contemporary volatile anesthetics can initiate MH, but halothane is the most potent triggering agent relative to other inhalation anesthetics.[263] The syndrome is characterized by a rapid rise in body temperature that, if not treated quickly, causes death. Monitoring of temperature and CO_2 production is warranted in susceptible or suspected patients. Patients known to be susceptible to MH can be anesthetized safely. Avoiding the use of triggering agents and administering prophylactic dantrolene before anesthesia are effective in preventing the onset of MH.[263]

Further discussions on the clinical pharmacology and use of volatile inhalant anesthetics in various species and disease conditions, and for special procedures and patients, can be found in other sections of this book that emphasize individual anesthetic patient management.

The Gaseous Anesthetic: Nitrous Oxide

Nitrous oxide was introduced into clinical practice more than 150 years ago. Since then, its use has formed the basis for the use of more general anesthetic techniques in human patients than any other single inhalation agent.[19] Its use became widespread because of its many desirable properties, including low blood solubility (Table 13.2), limited cardiovascular and respiratory system depression, and minimal toxicity.[19] Its use in the anesthetic management of animals became a natural extension of its use in people.

Dose

Nitrous oxide is not the ideal anesthetic for people or animals. As discussed earlier in this chapter, N_2O is not a potent anesthetic (Table 13.7a and b) and will not anesthetize a fit, healthy individual. To derive the important benefits from the use of N_2O, it is usually administered in high inspired concentrations. However, as the concentration of N_2O is increased, there is a change in the proportion and partial pressure of the various other constituents of the inspired breath, notably O_2. Consequently, to avoid hypoxemia, 75% of the inspired breath is the highest concentration that can be administered safely under conditions at sea level. Use of N_2O at locations above sea level requires a lower N_2O concentration to ensure an adequate partial pressure of inspiratory O_2 (PiO_2). Nitrous oxide has less value in the anesthetic management of animals than in that of human patients because the anesthetic potency of N_2O in animals is only about half that found for humans (e.g., the MAC for dogs is about 200% vs. about 100% for people [Table 13.7a]).[10,216] Thus, the value of N_2O in veterinary clinical practice is primarily as an anesthetic adjuvant, that is, accompanying other inhaled or injectable drugs. Since the effects of N_2O on vital organ function (including cardiovascular and respiratory) in the absence of hypoxemia are small in most veterinary patients, benefit is afforded by enabling a certain reduction in the amount of the primary, more potent, inhaled or injectable anesthetic agent.

Kinetics

Nitrous oxide's low blood solubility (Table 13.2) is responsible for a rapid onset of action. Although it does not have the potency to produce anesthesia, it may be used to speed induction of inhalation anesthesia as a result of its own (albeit limited) CNS effects and, as mentioned earlier, also by augmenting the uptake of a concurrently administered more potent volatile anesthetic such as halothane: the second gas effect.[10,19,274,275] When a high concentration of N_2O is administered concurrently in a mixture with an inhalation agent (e.g., N_2O plus halothane), the alveolar concentration of the simultaneously administered anesthetic (halothane) increases more rapidly than when the "second" gas has been administered without N_2O. The second gas effect is the result of an increased inspiratory volume secondary to the large volume of N_2O taken up (remember, N_2O is used at high concentrations)[274] and a concentrating effect on the second gas in a smaller volume (and thus increased gradient for transfer to blood) as a result of the uptake of the large volume of N_2O.[10,275] Results of a more recent study with desflurane confirms previous findings for the second gas effect.[276]

Pharmacodynamics

As noted previously, N_2O's effects on cardiovascular and respiratory function (other than reducing the inspired O_2 concentration) are small compared with other inhalation anesthetics. It does depress myocardial function directly, but its sympathetic stimulation properties counteract some of the direct depression (its own as well as that from accompanying volatile anesthetics).[216] As a result of its sympathetic nervous system activation it may contribute to an increased incidence of cardiac arrhythmias.[277,278] There is evidence to suggest that its use contributes to myocardial ischemia in some circumstances.[279–282] Overall, a conservative outlook regarding N_2O use relative to respiration and circulation is that significant concern is warranted only in patients with initially compromised function.[283,284] As with any agent, its advantages and disadvantages should be weighed on an individual patient basis.

Nitrous oxide has little or no effect on liver and kidney function.[285–287] Although there is evidence of N_2O-induced interference with the production of red and white blood cells by bone marrow, the risk of adverse outcomes to a patient exposed under most clinical veterinary circumstances is little or none.[286,288] However, prolonged exposure to N_2O causes megaloblastic hematopoiesis

and polyneuropathy. Seriously ill patients may have increased sensitivity to these toxicities. Problems result from N_2O-induced inactivation of the vitamin B_{12}–dependent enzyme methionine synthase, an enzyme that controls interrelations between vitamin B_{12} and folic acid metabolism.[289] Although an occasional patient may develop signs suggestive of vitamin B_{12} and folic acid deficiency after an anesthetic technique that includes the use of N_2O, this is a rare event in human and animal patients.[286,290] Prolonged occupational or abusive exposure to N_2O may be equally harmful, and this potential harm should be considered in management plans of veterinary practices.[32,286,291,292] Nitrous oxide is rapidly and mainly eliminated in the exhaled breath. The extent of biotransformation (to molecular nitrogen [N_2]) is very small and mainly by intestinal flora[32,293,294] (Table 13.6).

Transfer of Nitrous Oxide to Closed Gas Spaces

Gas spaces exist or may exist in the body under a variety of conditions and to varying degrees. For example, gas is normally found in the stomach and intestines. The gut is a dynamic reservoir; the gas it contains is freely movable into and out of it according to the laws of diffusion. The gas in the gut originates from air swallowing, normal production of bacterial behavior, chemical reactions, and diffusion from the blood. There is marked variability in both composition and volume of stomach and bowel gas (e.g., herbivore vs. carnivore). There are other natural air cavities, such as the air sinuses and the middle ear, and then there are circumstances in which air may be electively or inadvertently introduced as part of diagnostic or therapeutic actions (e.g., pneumoencephalogram, pneumocystogram, endoscopy, and vascular air emboli).

Potential problems associated with gas spaces arise when an animal breathing air is given a gas mixture containing N_2O.[10,19] Nitrogen is the major component of air (80%) and of most gas spaces (methane, CO_2, and hydrogen are also found in variable quantities in the gut). When N_2O is introduced into the inspired breath, a reequilibration of gases in the gas space begins with N_2O quickly entering and N_2 slowly leaving. That is, because of its greater blood solubility, the volume of N_2O that can be transported to a closed gas space is many times the volume of N_2 that can be carried away.[10] For example, the blood-gas PC for N_2O is 0.47 (Table 13.2), whereas that for N_2 is about 0.015.[295] Thus, N_2O is more than 30 times more soluble in blood than is N_2 (0.47/0.015). The result of the net transfer of gas to the gas space can be manifested as an increase in volume, as with the gut,[296,297] pneumothorax,[297] or blood embolus;[298,299] an increase in pressure (e.g., middle ear[300,301] or pneumoencephalogram[302]); or both (as the distending limits of the compliant space are reached). Usually air is used to inflate the cuff of an endotracheal tube. This cuff is another relatively compliant, enclosed air space. Nitrous oxide will similarly expand this gas space and may increase the pressure exerted on the tracheal wall.[303–305]

Diffusion Hypoxia

A further issue requiring consideration for the differential movement of N_2O and N_2 is at the end of anesthesia when N_2O is discontinued. Because of the large volume of N_2O stored in the body during anesthesia and the unequal change of N_2O for N_2, a deficiency in blood oxygenation may occur at the end of anesthesia if air is abruptly substituted for N_2O. As discussed earlier in this chapter, this condition is referred to as *diffusion hypoxia*.[35,36] The rapid outpouring of N_2O from the blood into the lung causes a transient but marked decrease in alveolar PO_2, with a resultant decrease in PaO_2.

Interaction with Respiratory Gas Monitoring

Routine monitoring of expired CO_2 is increasingly important and possible in the operating room of veterinary hospitals. Nitrous oxide interferes with the accurate recording of CO_2 with some monitoring devices. This interaction must be considered in decisions regarding the purchasing of equipment and overall anesthetic management plan. A more complete summary of the advantages and disadvantages of N_2O use is available elsewhere.[19] Brief summaries of practical considerations of N_2O use in veterinary practice have also been published.[306,307]

Occupational Exposure: Trace Concentrations of Inhalation Anesthetics

Operating-room personnel are often exposed to low concentrations of inhalation anesthetics. Ambient air is contaminated via vaporizer filling, known and unknown leaks in the patient breathing circuit, and careless spillage of liquid agent. Measurable amounts of anesthetic gases and vapors are present in operating-room air under a variety of conditions.[308–315] Personnel inhale and, as shown by studies, retain these agents for some time.[316,317] The slow rate of elimination of some vapors (especially the more blood-soluble agents like halothane) enables retained trace anesthetic quantities to accumulate from one day to the next.

Concern is raised because epidemiological studies of humans and laboratory studies of animals have suggested that chronic exposure to trace levels of anesthetics may constitute a health hazard. The possibility that chronic exposure to low levels of anesthetic agents constitutes a hazard to health science personnel has attracted and maintained worldwide interest since the early 1970s. Of particular concern are reports that inhaled anesthetics possess mutagenic, carcinogenic, or teratogenic potential. Depending on the point in life at which exposure occurs, there is concern that these underlying mechanisms in turn may be responsible for an increased incidence of fetal death, spontaneous abortion, birth defects, or cancer in exposed workers.[318–320] However, to date, no genotoxic effect of long-term or short-term exposure to inhaled anesthetics has been demonstrated in humans, and "the conclusion from both animal and human studies is that there is no carcinogenic risk either from exposure to the currently used inhaled anesthetics."[32]

Although the data to date, especially regarding effects on human reproduction, remain equivocal, a firm cause-and-effect relationship between chronic exposure to trace levels of anesthetics and human health problems does not exist. Although the risk

Table 13.12. Methods to reduce occupational exposure to inhalation anesthetics in the operating room

1. Use waste gas *scavenger* to collect gas from the pressure-relief (pop-off) valve of the patient breathing circuit and ventilator
2. Conduct *regular inspection* and *maintenance* to detect and repair leaks in anesthetic machines and patient breathing circuits, piped gas supplies (nitrous oxide), etc.
3. *Alter work practices* (e.g., minimize leaks around the face mask and turn off the vaporizer and fresh gas flow when the patient breathing circuit is not attached to the patient)
4. Ventilate operating rooms adequately
5. Monitor room trace anesthetic gas levels
6. Educate personnel

of long-term exposure to trace concentrations of anesthetics for those in operating-room conditions appears minimal, current evidence is suggestive enough to cause concern and to encourage practices to reduce the contamination by anesthetics of operating-room personnel. Indeed, exposure levels have been recommended by the government: 2.0 parts per million (ppm) for volatile agents and 25 ppm for N_2O.[318] In this regard, inexpensive methods to reduce and control anesthetic exposure by operating-room personnel are available and should be used (Table 13.12).

Frequent monitoring of actual levels of anesthetic gas or vapor is of obvious value and is encouraged in specialized circumstances and/or environments where there is high use. Likely the greatest impact results from educating personnel about the potential problem of waste anesthetic gases and methods for controlling exposure levels.[318–321] For further information on this subject, readers are directed to a more complete report of current knowledge and conclusions from available data that have been developed by the American Society of Anesthesiologists (ASA) Task Force on Trace Anesthetic Gases of the ASA Committee on Occupational Health of Operating Room Personnel.[322]

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