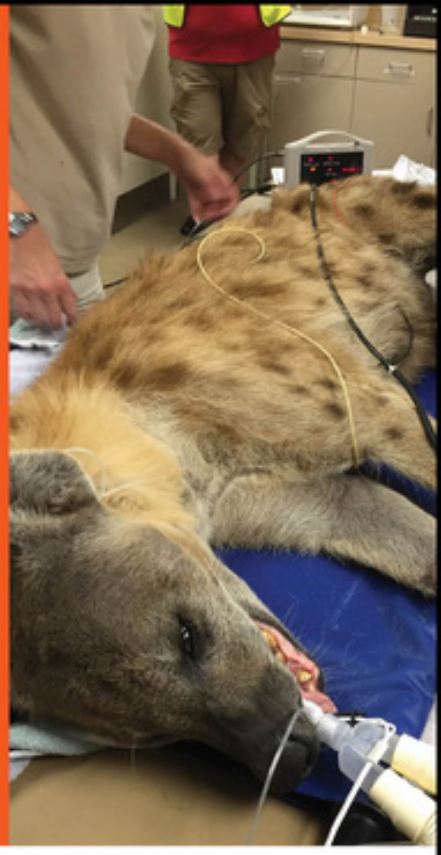
Third Edition

Zoo Animal and Wildlife Immobilization and Anesthesia



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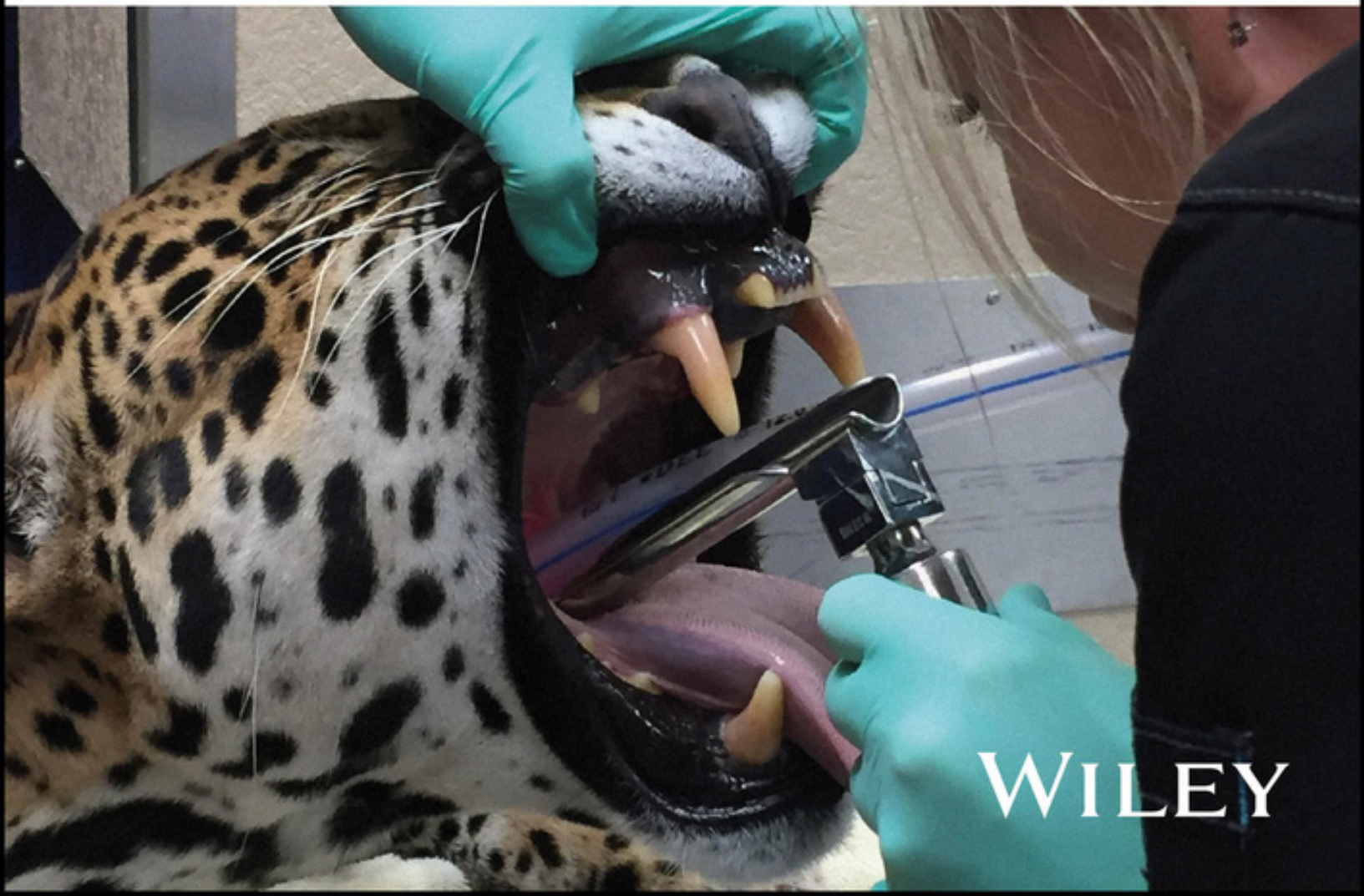

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Preface

Welcome to the third edition of *Zoo Animal and Wildlife Immobilization and Anesthesia*. This edition was developed at a time of great clinical and research advances in the anesthesia of wildlife. The goal of this work was to develop a textbook that promotes best practices in anesthesiology and supports the efficient acquisition and sharing of knowledge. We realize there is some redundancy, but we have tried to reduce repetition wherever possible. Clinical problems are often managed differently, and we understand that clinical experience may influence the decision-making process in anesthesia. We hope that this textbook will also continue to help practitioners prepare for board certification.

We have many new contributors in the third edition, and this has offered a fresh point of view on many subjects.

We want to express our sincere appreciation to all of our contributors who have allowed us to deliver an outstanding new edition.

Gary West, Darryl Heard, and Nigel Caulkett

1

Clinical Pharmacology

Leigh A. Lamont and Kurt A. Grimm

Introduction

Pharmacology is the study of drugs and their interactions with organisms (Page & Maddison 2002). Pharmacology incorporates aspects of statistics, biochemistry, biology, pathology, and medicine. Failure to interpret the description of drugs' pharmacological properties in the context of the clinical picture (i.e., clinical pharmacology) can result in unintended outcomes.

The pharmacological data available for most drugs are mean values derived from a relatively small number of individuals (usually healthy individuals). While this approach provides a starting point for clinical use of drugs, individual responses can vary greatly due to disease states, body condition, environment, genetics, coadministered drugs, and many other factors. When the toxic dose is close to the therapeutic dose (as is often the case with drugs used for immobilization and anesthesia), careful titration of dose and patient monitoring are required. However, the nature of working with wildlife and captive nondomestic species often precludes baseline health assessment, individualization of dosing, and intensive patient monitoring. This is one factor associated with increased risk of adverse outcomes when capturing or anesthetizing nondomestic species. It should also be appreciated that advances in drug safety will likely result in only limited improvement of the safety of anesthesia and immobilization. Management of other risk factors through airway management, reduction of stress, and improvements in supportive care will also be beneficial.

Pharmacokinetics

Pharmacokinetics can be generally defined as what an organism does to a drug. Absorption, distribution, biotransformation, and elimination are processes which determine the concentration of drug at the site of action (i.e., biophase). Pharmacokinetic parameters are estimates of these processes in the group of animals studied. These estimates can be used to predict or understand the way a drug interacts with an organism. It is important to understand that pharmacokinetic parameters can vary between individual animals and can be influenced by many different drug- and organism-related factors. Additionally, pharmacokinetic parameters are derived using mathematical models selected by the investigator. There is usually no correlation between model components and anatomical structures.

Pharmacodynamics

Pharmacodynamics can be generally defined as what a drug does to an organism. Pharmacodynamics includes intended drug effects as well as adverse drug actions. Drugs such as opioids, alpha-2 adrenergic agonists, and antimuscarinics act by binding to relatively well-characterized receptor complexes located on cellular membranes and produce well-characterized effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production by binding to cyclooxygenase enzyme isoforms. Relating plasma drug concentrations to observed NSAID actions can be complex in comparison to other drugs (e.g., opioids) due to the different nature of the action. Preexisting prostaglandins, as well as the slower process of inhibiting an enzyme system, confound the relationship between drug concentration and effect. The molecular and neurophysiologic actions of inhalant anesthetics, in contrast, have not been completely characterized even though the drugs have been used clinically for many years and their pharmacodynamic effects have been well described (Steffey et al. 2015).

Zoo Animal and Wildlife Immobilization and Anesthesia, Third Edition. Edited by Gary West, Darryl Heard, and Nigel Caulkett.

Pharmacodynamic effects are predictable for most clinically used drugs. However, individual animal responses can vary considerably. Additionally, the nature of capture of free-ranging and captive wildlife often makes accurate dosing and drug delivery difficult or impossible. Therefore, close monitoring of patient response and preparation for supportive care are paramount to safe immobilization and anesthesia.

Inhalant Anesthetics

Inhalant anesthetics are commonly used in companion animal veterinary practice. Their use under field conditions is limited due to the requirement for specialized delivery devices and a supply of delivery gas (e.g., oxygen). However, inhalant anesthetics are used commonly in controlled settings such as zoological parks and research laboratories because of the ease of titration of anesthetic depth and rapidity of recovery. Inhalant anesthetics should be delivered by a well-maintained anesthetic machine and properly trained individuals. While inhalant anesthetics are relatively safe, their low therapeutic index mandates frequent and careful monitoring of anesthetic depth.

Physics of Gases and Vapors

An understanding of the processes which influence the uptake and delivery of inhalant anesthetics allows the anesthetist to predict and respond to individual circumstances.

Brief Review of Molecular Theory

Molecules in a liquid state have more vibrational energy than when in a solid state, and each molecule can move through the liquid. If heat is added to a liquid, each molecule gains more kinetic energy and eventually some overcome the forces exerted by their neighbors and escape into the space above the liquid. This state is that of a gas or a vapor. A gas is a phase of matter that expands indefinitely to fill a containment vessel. A vapor is the gaseous state of a material below its boiling point.

A vapor is in equilibrium with the liquid beneath it. Because both gaseous and liquid molecules have kinetic energy, they are in constant motion. The molecules in the vapor phase are striking the liquid–gas interface and returning to the liquid, while liquid molecules are leaving the interface to become vapor. The relationship between these two phases depends mainly on the physicochemical properties of the molecules and the temperature of the system.

Vapor Pressure

Molecules in a gaseous state possess kinetic energy and collide with the walls of the containment vessel. These collisions produce a force on the walls. This force is spread over a surface area and therefore is a pressure (pressure = force/area). This pressure is called the vapor pressure. Since kinetic energy increases directly with temperature, vapor pressure must always be given with reference to the temperature it was measured at (e.g., vapor pressure of water is 47 mmHg at 37°C).

When many gases are present in a mixture, such as with atmospheric air or during delivery of inhalant anesthetics, each gas has a vapor pressure that is independent of the other gases (Dalton's law of partial pressures). It is convention to refer to vapor pressure as partial pressure under these conditions. Partial pressure of an anesthetic agent is analogous to the concept of "free drug" and is important for determining the effect of the anesthetic (e.g., the level of central nervous system (CNS) depression correlates directly with the partial pressure of isoflurane within the brain) (see Table 1.1) (Steffey et al. 2015).

Vapor Concentration

Vapor (i.e., partial) pressure is important for the observed pharmacological effect of inhalant anesthetics. However, almost all anesthesiologists refer to the amount of anesthetic delivered in units of volumes % (said as volumes-percent), or just percent, which is a concentration. The fundamental difference between anesthetic partial pressure and anesthetic concentration is that partial pressure relates to the absolute number of molecules and their kinetic energy whereas concentration refers to the number of molecules of anesthetic relative to the total number of molecules present.

Table 1.1 Anesthetic agent vapor pressures at 20 and 24°C.

Anesthetic Agent	Vapor Pressure @ 20°C in mmHg	Vapor Pressure @ 24°C in mmHg
Methoxyflurane	23	28
Sevoflurane	160	183
Enflurane	172	207
Isoflurane	240	286
Halothane	243	288
Nitrous oxide	Gas	Gas

Source: Adapted from Steffey EP, Mama KM, Brosnan RJ. 2015. Inhalation anesthetics. In: *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (KA Grimm, KA Lamont, WJ Tranquilli, SA Greene, SA Robertson, eds.). Ames: Wiley Blackwell.

Critical Temperature

The critical temperature is the temperature above which a substance cannot be liquefied no matter how much pressure is applied. The critical temperature of nitrous oxide is 36.5°C. Consequently, nitrous oxide can be (and is) a liquid below this temperature, but is a gas at greater temperatures. Placing a nitrous oxide tank near a heat source will result in volatilization of liquid nitrous oxide, resulting in a high tank pressure and danger of explosion or tank venting.

The critical temperature of oxygen is −119°C, therefore at room temperature oxygen cannot be liquefied. All compressed cylinders of medical oxygen contain only gas. There are liquid oxygen tanks, but the internal tank temperature is below −119°C.

Henry's Law

Henry's law states the solubility of a gas in a liquid is proportional to the pressure of the gas over the solution. It describes the solubility of an anesthetic in body fluids or other liquids. From it you can derive the formula $c = k \cdot P$, where c is the molar concentration (mol/L) of the dissolved gas and P is the pressure (in atmospheres) of the gas over the solution. For a given gas k is the Henry's law constant and is dependent on temperature.

Partition Coefficient

A partition coefficient is the ratio of the concentration of a substance in one medium relative to another at equilibrium. It is related to the solubility of an agent. At equilibrium the partial pressure is the same throughout the body, including the alveolar gas, but the concentration of total drug may be very different due to partitioning into tissues or body fluids (Table 1.2) (Steffey et al. 2015). Partition coefficients are not absolute constants for an anesthetic agent. Tissue composition may change as a function of age, sex, body condition, etc. and these changes may influence partitioning.

Table 1.2 Selected partition coefficients of commonly used anesthetic agents.

Anesthetic	Blood:Gas Partition Coefficient	Brain:Blood Partition Coefficient
Nitrous oxide	0.47	1.1
Desflurane	0.42	1.3
Enflurane	2.00	1.4
Sevoflurane	0.68	1.7
Methoxyflurane	15.0	2.0
Isoflurane	1.46	2.7
Halothane	2.54	2.9

Source: Adapted from Steffey EP, Mama KM, Brosnan RJ. 2015. Inhalation anesthetics. In: *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (KA Grimm, KA Lamont, WJ Tranquilli, SA Greene, SA Robertson, eds.). Ames: Wiley Blackwell.

Mechanism of Action of Inhaled Anesthetics

The simplest definition of general anesthesia is a reversible drug-induced loss of consciousness (Franks 2006). All clinically used injectable and inhaled general anesthetics reversibly induce unconsciousness at low concentrations and induce an increasing lack of responsiveness at higher concentrations (Franks 2006). Though there are a number of other desirable clinical end-points including amnesia, analgesia, immobility and muscle relaxation (Brown et al. 2010), commonly used anesthetics vary in their ability to produce these effects. Consequently, any explanation of anesthetic mechanism of action must focus on unconsciousness as the critical end-point.

Despite their longstanding and widespread use, and well-characterized pharmacodynamic effects, the specific molecular and neurophysiologic mechanisms of action of general anesthetics are only now beginning to be elucidated thanks to research accumulated over the past 120 years.

The first widely accepted theory of general anesthesia was published by Meyer and Overton in 1901. They observed that most anesthetics were lipophilic and highly hydrophobic and noted a correlation between an anesthetic's potency and the agent's oil–gas partition coefficient (Meyer 1901; Overton 1901). The so-called Meyer–Overton correlation formed the basis for numerous lipid bilayer hypotheses of anesthetic action that dominated the literature until the 1970s.

Franks and Leib were among the first to question the unitary hypothesis that the lipid bilayer was the sole site of anesthetic action (Franks & Leib 1978). They subsequently published their seminal work demonstrating that the Meyer–Overton correlation was preserved for inhibition of firefly luciferase, a soluble lipid-free model protein (Franks & Lieb 1984), which gave rise to the protein receptor hypothesis of general anesthesia. While many potential protein targets have been studied, strong evidence for direct involvement in anesthetic-induced loss of consciousness currently exists for only three: gamma-aminobutyric acid subtype A ($GABA_A$) receptors, two-pore-domain potassium (2PK) channels, and N-methyl-D-aspartate (NMDA) receptors (Uhrig et al. 2014; Chau 2010; Franks 2008).

The $GABA_A$ family of receptors is responsible for most of the fast neuronal inhibition in the mammalian CNS and enhanced GABA-activated chloride currents cause hyperpolarization of neuronal membranes and reduce neuronal activity. Almost all general anesthetics have been found to potentiate GABA-induced chloride currents but are only

capable of directly activating $GABA_A$ receptors at much higher, clinically irrelevant concentrations. Several different mutations in the alpha subunits of the $GABA_A$ receptor have been shown to eliminate or reduce the effects of volatile anesthetics (Mihic et al. 1997; Krasowski & Harrison 2000; Jenkins et al. 2001, 2002; Nishikawa & Harrison 2003; Forman & Miller 2016), whereas those in the beta subunits can reduce the effects of both intravenous and volatile anesthetic agents (Krasowski & Harrison 2000). Experiments demonstrating a correlation between stereoselectivities seen in genetically modified animals in vivo and those found with extrasynaptic $GABA_A$ receptors in vitro provide convincing evidence that these receptors play an important role in volatile anesthetic-induced loss of consciousness (Franks 2008).

The 2PK channels are thought to provide "background" modulation of neuronal excitability. Five members of this channel family (TREK1, TREK2, TASK1, TASK3, and TRESK) can be directly activated by volatile anesthetics (Patel et al. 1999) but anesthetic sensitivity among these channels is not uniform. Anesthetic activation of 2PK channels generally inhibits neuronal activity by either hyperpolarizing the membrane and/or increasing membrane conductance, thus reducing the effects of excitatory currents (Franks 2008). However, these channels are also found presynaptically and their activation here may be inhibitory (if at an excitatory synapse) or excitatory (if at an inhibitory synapse). A growing body of evidence suggests these channels mediate at least some of the effects of volatile anesthetics (Franks 2008).

NMDA receptors mediate the slow components of synaptic transmission in the CNS and may be important targets for certain anesthetics. Both gaseous (i.e., xenon and nitrous oxide) and volatile (i.e., isoflurane, sevoflurane, halothane, and desflurane) inhaled anesthetics inhibit NMDA receptors to some extent but considerable variability exists among agents. Although it is likely that NMDA receptor antagonism plays a role in the actions of xenon and nitrous oxide and, to a lesser extent, the volatile agents, additional targets are required to account for their ability to cause loss of consciousness (Franks 2008).

Determining the cascade of events that follow binding of an anesthetic agent to its molecular target(s) leading to loss of consciousness has proven difficult. Remarkable advances in neuroscience and neuroimaging techniques (e.g., positron emission tomography, functional magnetic resonance imaging [fMRI], magnetoencephalography, and electroencephalography) over the past two decades are beginning to unravel the neural correlates of consciousness which will help answer this longstanding question.

Convergent evidence from multiple studies involving multiple species, multiple neuroimaging modalities, multiple analytic techniques, and diverse drug classes suggests that anesthetic-induced unconsciousness is characterized by a functional fragmentation (also referred to variably as a disconnection or uncoupling) of cortical and thalamocortical networks (Hudetz & Mashour 2016; Li et al. 2017; Mashour & Hudetz 2017). One specific cortical region, known as the lateral frontoparietal network, has received considerable attention over the last decade. Both fMRI and electroencephalographic studies of diverse classes of anesthetics, including volatile inhaled agents, consistently show a functional breakdown in frontoparietal connectivity and surrogates of frontoparietal information transfer (Hudetz & Mashour 2016; Mashour & Hudetz 2017). As our understanding of consciousness continues to evolve, traditional references to the "depth of anesthetic hypnosis" may require revision to reflect the fact that general anesthetics may variably suppress certain higher-order components of consciousness while retaining others (Sleigh et al. 2018).

Inhalant Anesthetic Pharmacokinetics

Anesthetic Uptake and Distribution

A series of partial pressure gradients, beginning at the vaporizer, continuing in the anesthetic breathing circuit, the airways, alveoli, blood, and ending in the tissues will drive the movement of an anesthetic gas. The movement of that gas will continue until equal partial pressures are present throughout the system. Since the lung is the point of entry and exit to the body, the alveolar partial pressure governs the partial pressure of the anesthetic in all body tissues. Therefore, it is most important to understand how to influence the alveolar partial pressure. Increasing alveolar minute ventilation, flow rates at the level of the vaporizer, and inspired anesthetic concentration can speed the delivery of anesthetic and increase the rate of rise of alveolar anesthetic partial pressure. Solubility, cardiac output, and the alveolar-to-venous anesthetic gradient are factors that determine the uptake of the anesthetic from the alveoli into the blood. Solubility describes the affinity of the gas for a medium such as blood or adipose tissue and is reported as a partition coefficient. The blood/gas partition coefficient describes how the gas will partition itself between the two phases (blood and alveolar gas) after equilibrium has been reached. Isoflurane, for example, has a blood/gas partition coefficient of approximately 1.46 (Steffey et al. 2015). This means that if the gas partial pressures are in equilibrium, the concentration in blood will be 1.46 times greater than the concentration in the alveoli. A higher blood/gas partition coefficient means a greater uptake of the gas into the blood, therefore a slower rate of rise of alveolar and blood partial pressure. Since the blood partial pressure rise is slower, it takes longer for the brain partial pressure of the gas to increase, resulting in a longer induction time.

Increased cardiac output exposes the alveoli to more blood per unit time. The greater volume of blood removes more inhalant anesthetic from the alveoli, therefore lowering the alveolar partial pressure. The agent might be distributed faster within the body, but the partial pressure in the arterial blood is lower. It will take longer for the gas to reach equilibrium between the alveoli and the brain, therefore a high cardiac output usually prolongs induction time. The alveolar to venous partial pressure difference reflects the tissue uptake of the inhaled anesthetic. A large difference is caused by increased uptake of the gas by the tissues during the induction phase.

Transfer of the gas from the arterial blood into tissues such as the brain will depend on perfusion and the relative solubility of the gas in the different tissues. The brain/blood coefficient describes how the gas will partition itself between the two phases after equilibrium has been reached. Isoflurane has a brain/blood coefficient of 2.7, therefore when the system is at equilibrium the concentration in the brain will be 2.7 times greater than the concentration in the blood (Steffey et al. 2015). All contemporary inhalation anesthetics have high adipose/blood partition coefficients. This means that most of the gas will accumulate in adipose tissue as times goes by. The partial pressure of the gas in adipose tissue will rise very slowly since this tissue has a high capacity (as indicated by the high adipose/blood partition coefficient). Inhalation anesthetics stored in obese patients may delay awakening at the end of long periods of anesthesia. Fortunately, adipose tissue has a relatively low blood flow and doesn't accumulate significant amounts of anesthetic during the short periods of anesthesia commonly encountered in veterinary medicine.

Elimination of Inhaled Anesthetics

The rate of induction and recovery from anesthesia with inhalant anesthetics differs between agents due to differences in tissue solubility, but general statements can be made. During induction all tissue partial pressures are zero. During recovery, different tissues in the body have different partial pressures of anesthetic, which are governed by the tissue anesthetic content and not the alveolar partial pressure. Recovery is not as controllable as induction of anesthesia. During recovery from anesthesia, elimination occurs due to exhalation and biotransformation.

The enzymes responsible for inhalant anesthetic metabolism are mainly located in liver and kidneys. Anesthetic elimination via metabolism is approximately 50% for methoxyflurane, 10–20% for halothane, 5–8% for sevoflurane, 2.5% for enflurane, about 0.2% for isoflurane, 0.001% for desflurane, and nearly zero for nitrous oxide (Steffey et al. 2015). The amount of anesthetic eliminated from the body during anesthesia due to metabolism is small compared with the amount exhaled. However, anesthetic metabolism accounts for a larger proportion of the anesthetic clearance after anesthetic delivery ceases. The low, but prolonged, blood partial pressure of the anesthetic found after terminating delivery is no longer overwhelming the enzyme systems (enzymes become saturated above ~1 MAC [minimum alveolar concentration]) so metabolism accounts for a larger proportion of clearance than it did during exposure to high partial pressures.

Elimination of the anesthetic via the lungs can be complex. The first point to consider is what effect an increase in alveolar minute ventilation will have on recovery. During recovery, increasing minute ventilation will decrease alveolar anesthetic partial pressure and increase the gradient for diffusion from the blood to the alveoli. This increases elimination, especially for most anesthetic agents with high blood/gas partition coefficients.

Another situation to consider is what effect a change in cardiac output will have on the rate of decrease of partial pressure of the inhalant anesthetic. During induction, high cardiac output will increase the rate at which anesthetic is removed from the lung, slowing the rate of rise of anesthetic partial pressure and slowing induction. When cardiac output is reduced (e.g., cardiogenic shock) there is a slower removal of anesthetic and subsequently a faster rate of rise of alveolar partial pressure and induction occurs. During recovery a high cardiac output will increase the rate at which anesthetic is returned to the lung for excretion. Since the partial pressure of anesthetic in the blood is determined by the tissues, the higher blood flow will shorten recovery. During low cardiac output situations there will be a slower recovery due to the decreased rate at which tissue anesthetic partial pressure decreases.

The last major influence on the rate of induction and recovery is the solubility of the anesthetic agent. Agents with high blood/gas solubility will be partitioned into the blood to a greater extent than agents with low blood/gas solubility. The blood acts as a depot for agent maintaining anesthetic partial pressure. Agents with low blood/gas solubility do not partition into the blood to the extent of highly soluble agents, thus the decrease in partial pressure is faster and recovery time is reduced. Highly soluble agents have high blood concentrations and it will take longer for the partial pressure to decrease if all other factors are equal. In summary, elimination of a volatile anesthetic depends on the ventilation, cardiac output, and solubility of the gas in blood and tissue.

Control of the Partial Pressure of Delivered Anesthetic

Inhalant anesthetics can be classified as either gaseous (nitrous oxide and xenon) or volatile (isoflurane, sevoflurane, halothane, methoxyflurane, and desflurane). Gaseous

anesthetics are usually delivered to the anesthesia machine under pressure and their rate of delivery to the breathing circuit is controlled by a flow meter. Volatile anesthetics are liquids at room temperature and pressure, and are usually delivered by a specialized apparatus that controls the volatilization of the liquid and proportioning of the vapor in the fresh gas delivered to the patient. A vaporizer can be as simple as piece of cotton soaked with agent held near the nose (not recommended) or can be as complex as the desflurane vaporizer, which is an electrically powered device with a heated vaporizing chamber.

The Breathing System

With most modern anesthetic machines the outflow gas from the vaporizer will be delivered to the patient through a set of tubes and machinery collectively called a breathing system. There are many styles of breathing systems, each with a multitude of uses. It is important that the anesthetist understands how the type of breathing circuit used will impact the rate at which the anesthetic concentration can be changed and the relationship between the vaporizer setting and inspired concentration.

Waste Anesthetic Gases

The health effects of chronic exposure to waste anesthetic gases are not completely known. The frequency of inhalant anesthetic use and the lack of significant associations between exposure and most types of chronic toxicities (e.g., cancer, infertility, birth defects, etc.) would suggest there is only a very low risk (if any) associated with chronic exposure. However, certain individuals are highly susceptible to potentially life-threatening reactions, even with trace level exposure (e.g., malignant hyperthermia). In light of this, and with the admission that we do not completely understand all the risks associated with chronic exposure, it is generally agreed that the exposure of personnel be kept as low as reasonably acceptable (ALARA). In the United States, the Occupational Safety and Health Administration requires veterinary hospitals to maintain a system to prevent waste gases from building up in the area of use and can enforce exposure limits that are consistent with guidance from the National Institute of Occupational Safety and Health (NIOSH). Currently, no NIOSH–recommended exposure limits exist for the three most currently used anesthetics (isoflurane, desflurane, and sevoflurane) and at present NIOSH has no published permissible exposure limits regulating these specific agents (American Veterinary Medical Association 2020).

Minimum Alveolar Concentration

Although loss of consciousness is arguably the most critical end-point of general anesthesia (see section on the inhaled anesthetic mechanism of action), it remains challenging to measure in a clinical setting. Immobility in the face of a noxious stimulus is also an important end-point and has formed the basis of the standard unit of inhaled anesthetic potency – minimum alveolar concentration (MAC) – since the 1960s (Merkel & Eger 1963). While our understanding of how inhaled anesthetics produce immobility continues to evolve (Eger et al. 2008), MAC remains the standard measurement of dose in clinical anesthesia. It is defined as the minimum alveolar concentration at 1 atmosphere required to prevent gross purposeful movement in 50% of the subjects tested, following a 60-second application of a supramaximal stimulus (Steffey et al. 2015). One MAC is by definition the EC_{50} (i.e., the effective concentration in 50% of patients) for that agent. Animals awaken from anesthesia at approximately 0.5 MAC, surgical anesthesia occurs at approximately 1.3 MAC, and severe autonomic nervous system depression occurs around 2 MAC.

Birds and many reptiles do not have true alveoli so the concept of MAC has been modified or redefined to be the minimum anesthetic concentration. It is not identical to MAC from other species, but closely approximates it in many ways.

Physiological and Pharmacological Factors That Alter MAC

Minimum alveolar concentration is age-dependent, being lowest in newborns, reaching a peak in infants, and then decreasing progressively with increasing age (Lerman et al. 1983, 1994; Taylor & Lerman 1991). Increases in MAC can also occur from hyperthermia and hypernatremia, and decreases in MAC can result from hypothermia, hyponatremia, pregnancy, hypotension, and drugs such as lithium, lidocaine, opioids, and alpha-2 adrenergic agonists.

General Pharmacological Actions of Inhalant Anesthetics

Inhalant anesthetic agents have more similarities than differences with respect to their effects on vital organ systems. The differences are primarily related to the speed and magnitude with which the changes occur. There are a few classic differences that have been included in the following synopsis.

Central Nervous System

All inhalant general anesthetics alter consciousness, memory, and pain perception by acting on the CNS. Most inhalant anesthetics cause a mild to moderate decrease in the cerebral metabolic requirement for oxygen ($CMRO_2$) and they usually have minimal effects on cerebral blood flow autoregulation at low MAC multiples (Mielck et al.

1998, 1999). Patients with intracranial hypertension should not be anesthetized with nitrous oxide because it may cause an increase in $CMRO_2$ (Roald et al. 1991; Algotsson et al. 1992; Hoffman et al. 1995). Halothane is also a poor choice because of its significant effects on cerebral blood flow autoregulation (Steffey et al. 2015). Isoflurane, sevoflurane, and desflurane are the inhalants of choice.

Cardiovascular System

Most inhalant anesthetic agents cause direct myocardial depression. Halothane is the most depressant on contractility, but it generally has the fewest effects on vascular resistance (Steffey et al. 2015). Isoflurane, enflurane, sevoflurane, and desflurane cause some degree of vasodilatation, which tends to improve forward blood flow and maintain tissue perfusion. The reduction in afterload also tends to offset some of the direct myocardial depressant effects and may result in a net improvement in cardiac output. Nitrous oxide is a sympathomimetic and can improve contractility, blood pressure, and heart rate at light levels of anesthesia. Rapid changes in anesthetic concentration (especially with desflurane) may result in a sympathetic response and temporarily increase cardiac work.

Respiratory System

All anesthetics tend to depress the chemoreceptor response to carbon dioxide, leading to an accumulation of carbon dioxide and a respiratory acidosis unless ventilation is assisted or controlled. The ether derivatives tend to be the most depressant, but all agents may cause significant depression. Most inhalant agents may interfere with hypoxic pulmonary vasoconstriction and may worsen ventilation-perfusion matching in the lung. This is most dramatic in larger animals, where significant pulmonary shunting is often observed.

Genital-Renal Systems

Most anesthetics cause a decrease in renal perfusion and an increase in antidiuretic hormone (ADH) secretion. Inhalant anesthetics may be the safest anesthetic techniques in anuric renal failure since pulmonary excretion is not dependent on renal function.

Inhalant anesthetics may cause an increase in postpartum uterine bleeding. This is a bigger consideration in primate anesthesia due to placentation characteristics. Isoflurane, sevoflurane, desflurane, and nitrous oxide have been advocated for use during Caesarian section because of the rapid onset and termination of effect, and the transient effects on the delivered fetuses. Methoxyflurane and halothane are less desirable due to their greater solubility and slower elimination.

Clinically Useful Inhalant Anesthetics

Nitrous Oxide

Nitrous oxide is commonly used in combination with a primary inhalant or injectable anesthetic drug. The reason it is not useful in veterinary anesthesia as a solo anesthetic is because of its low potency. Nitrous oxide's MAC value has been estimated to be near 100% for humans and closer to 200% for veterinary patients. It is obvious that 200% nitrous oxide cannot be delivered; in fact no more than 79% nitrous oxide can be safely delivered without creating a hypoxic gas mixture. In practice it is common to use a 50% nitrous oxide mixture with the balance of the mix being oxygen. If 50% nitrous oxide is delivered to an animal it is only providing approximately 0.25 MAC of anesthesia. A potent volatile anesthetic, injectable agent, or other sedative/analgesic drug must supply the remaining 0.75 MAC. Because of this limited anesthetic effect, nitrous oxide use for anesthetic maintenance is not widespread in veterinary medicine. Nitrous oxide is used by some anesthetists during induction of anesthesia for the *second gas effect*. Since nitrous oxide is present in the inspired gas mixture in a relatively high concentration and it rapidly diffuses into the body from the alveoli, the rate of rise of partial pressure of a second coadministered inhalant anesthetic is increased and the induction time can be shortened.

Nitrous oxide has a low blood/gas partition coefficient and has a rapid onset and recovery. The gas can diffuse out of the blood so rapidly that if nitrous oxide delivery is suddenly halted and supplemental oxygen is not administered, a situation known as *diffusion hypoxia* may result. Diffusion hypoxia happens when the mass movement of nitrous oxide down its partial pressure gradient results in high alveolar nitrous oxide partial pressure at the expense of oxygen and nitrogen partial pressures. Since breathing room air will result in an alveolar oxygen partial pressure of approximately 100 mmHg under ideal circumstances, any displacement of oxygen by nitrous oxide will result in alveolar hypoxia. Diffusion hypoxia can be minimized or prevented by continuing the administration of oxygen enriched gas for 5–10 minutes following the discontinuation of nitrous oxide. This helps because during normal breathing, 100% oxygen should result in an alveolar oxygen partial pressure close to 500 mmHg. The partial pressure of oxygen can drop a lot further before hypoxia develops.

Nitrous oxide is contraindicated in animals with pneumothorax, gastric dilatation/rumen tympany, gas embolism, and other conditions that are exacerbated by accumulation of gas inside a closed space. This effect is caused by diffusion of nitrous oxide out of the blood into the preexisting gas space in an attempt to establish equilibrium. Nitrous oxide is also contraindicated in animals with

gas diffusion impairment such as interstitial pneumonia. These animals typically have low arterial oxygen partial pressure when breathing oxygen-rich mixtures. The dilution of oxygen by nitrous oxide will lower the inspired oxygen partial pressure and may worsen hypoxemia.

Halothane

Halothane was a major advancement in inhalant anesthesia in its day. It was introduced in the late 1950s and was potent, nonirritating, and nonflammable. Chemically it is classified as a halogenated hydrocarbon and it is not chemically related to the ethers. Halothane was used widely in human anesthesia until it became apparent there were potentially fatal adverse effects associated with its use. Human patients developed a syndrome known as *halothane hepatitis* (Daghfous et al. 2003; Neuberger 1998). This rare, but life-threatening, complication is still somewhat of a mystery, although an immunological etiology is implicated. The disease appears as a fulminant hepatitis, similar to that seen with viral hepatitis, which develops after a short period of apparent recovery. A second, more common, form of hepatitis is less severe and is characterized by a reversible elevation in liver enzymes. The etiology of this second form is thought to be anesthetic-related hepatic hypoxia and does not appear to be immune related. Diagnosis of the correct form is important since repeated exposure to halothane, or any of the volatile agents producing trifluoroacetic acid, is more likely to trigger the immunologically mediated form and result in high morbidity and mortality. Both forms are not commonly documented in veterinary patients; however, transient elevation of liver enzymes may occur postoperatively in some patients. A thorough diagnostic workup is required due to the nonspecific and multifactorial etiology of elevated liver enzymes.

A second complication associated with halothane anesthesia is the development of arrhythmias. Halogenated hydrocarbon anesthetics, especially halothane, can sensitize the myocardium to the arrythmogenic effects of epinephrine. Halothane is generally contraindicated in patients that are predisposed to ventricular arrhythmias (e.g., hypoxia, trauma, or myocardial disease) (Steffey et al. 2015). Arrhythmias that develop during halothane anesthesia may resolve when the anesthetic agent is switched to isoflurane or sevoflurane. Other causes of perianesthetic arrhythmias should also be ruled out.

Halothane undergoes extensive hepatic metabolism (~20%) and is not chemically stable (Steffey et al. 2015). Commercially available halothane contains thymol, a preservative, which does not volatilize to the same degree as halothane. This results in a sticky residue inside the vaporizer that should be cleaned out during periodic maintenance. Veterinary use of halothane is declining due to the increasing popularity of isoflurane and sevoflurane, and its limited availability worldwide.

Isoflurane

Isoflurane is arguably the most widely used veterinary inhalant anesthetic in the world today. It is stable, potent, and undergoes little metabolism. Isoflurane can be irritating to airway tissues at high-inspired concentrations and its use for induction in people has been limited because of patient complaints and complications. However, in veterinary medicine isoflurane mask induction is still common. Isoflurane is a potent agent (MAC ~1.3% in dogs) and has a high saturated vapor pressure (~240 mmHg at room temperature) (Steffey et al. 2015). These characteristics, coupled with the fact that it is possible to cause rapid partial pressure changes in the brain, would suggest that only precision vaporizers located outside the circuit should be used to deliver the agent. However, several reports of the use of modified vaporizer inside circuit (VIC) vaporizers suggest that this type of anesthetic system can be used to safely administer the agent (Bednarski et al. 1993; Laredo et al. 1998).

Isoflurane metabolism is minimal (less than 1%) and fluoride-induced nephrotoxicity is uncommon. Isoflurane and many of the ether-derivative volatile agents are excellent vasodilators and can cause or worsen hypotension.

Desflurane

Desfluane use in veterinary medicine is limited to academic institutions and a very limited number of private practices. The main disadvantage to desflurane use is the cost associated with the agent and the cost associated with a specialized vaporizer that is required to deliver the drug. Desflurane is extremely insoluable and is capable of producing extremely rapid inductions and recoveries (Barter et al. 2004; Clarke 1999). Its main market is for human outpatient anesthesia, where rapid recovery is a large cost savings. It is highly fluorinated, has a very low potency (MAC ~9%), and has a high saturated vapor pressure (~670 mmHg at room temperature) (Steffey et al. 2015). Desflurane boils at 23°C and must be handled using specialized apparatus for vaporizer filling. The vaporizer is specific for desflurane and is electrically heated to boil the desflurane so that a reliable vapor pressure will be produced. Then sophisticated differential pressure transducers and electronic circuits calculate an injection ratio for delivery of the desired anesthetic concentration. Desflurane is very stable and undergoes almost no metabolism.

Sevoflurane

Sevoflurane is the newest volatile inhalant anesthetic approved for veterinary use. Sevoflurane has a low blood/gas partition coefficient (~0.7) which is greater than desflurane and nitrous oxide, but about half of that of isoflurane. Extensive pulmonary elimination of sevoflurane minimizes the amount available for metabolism. Up to 3–8% of the sevoflurane dose is metabolized and appears in the urine as inorganic fluoride (Steffey et al. 2015). This fluoride exposure does not appear to be clinically significant, although serum levels of fluoride can approach those previously reported to be nephrotoxic for methoxyflurane. Factors other than peak serum fluoride concentrations appear important for predicting the incidence of nephrotoxicity (Driessen et al. 2002).

Sevoflurane represents a deviation from the methyl ethyl ether structural theme present in other contemporary volatile anesthetics. Sevoflurane is chemically related to methyl-isopropyl ethers. The structure is significant because an important metabolite of most methyl-ethyl ether volatile anesthetic agents (trifluoroacetic acid) is a suspected trigger of halothane hepatitis. Sevoflurane cannot be metabolized to form this compound. This is not a major consideration in veterinary medicine but is important in human anesthesia. Sevoflurane is also pleasant and nonirritating when used for mask induction and many pediatric anesthesiologists suggest this agent is the drug of choice for pediatric induction via mask. Sevoflurane is less potent than isoflurane (MAC ~2.3% for dogs and horses). When used for induction of anesthesia it is common to use 7–9% sevoflurane.

An early subject of controversy surrounding sevoflurane anesthesia was the production of compound A. Compound A is a degradation product produced when sevoflurane reacts with the carbon dioxide absorbent. Early toxicology studies performed in rats suggested that proximal tubular renal damage could result from clinically relevant exposure to compound A. This led to the suggestion that sevoflurane should not be used in closed-circuit anesthesia or with fresh gas flow rates lower than 2 L per minute. However, since that time little clinical evidence of renal damage in humans and dogs has emerged, even with very low fresh gas flows. Some have suggested that rats have a 10–100 times higher level of the enzyme beta-lyase that is believed to convert the intermediate compounds of Compound A metabolism to a nephrotoxic molecule (Kharasch et al. 2005; Sheffels et al. 2004). Humans and dogs do not appear to have the same level of enzyme conversion and are therefore less susceptible to Compound A toxicity. Safety studies in most other rodents and exotic animals are not published and caution should be used when administering sevoflurane via a breathing system using a carbon dioxide absorbant until further safety data are available (Table 1.3).

Table 1.3 Structure and characteristics of inhalation anesthetics.

Agent	Year Introduced	Structure	Type
Halothane	1956	CF_3–CHClBr	Alkane
Isoflurane	1981	CF_3CHCl–O–CHF_2	Ether
Enflurane	1972	$CHClF$–CF_2–O–CHF_2	Ether
Methoxyflurane	1960	$CHCl_2$–CF_2–O–CH_3	Ether
Desflurane	1992	CF_3CHF–O–CHF_2	Ether

Injectable Anesthetics

Injectable anesthetics are an important family of compounds used for immobilization and anesthesia of wildlife. The dissociative anesthetics in particular are commonly combined with other adjunctive drugs such as alpha-2 adrenergic agonists and opioids to improve the reliability and speed of onset of action.

Barbiturates

Barbiturates can be classified in several ways. One is by chemical structure. Oxybarbiturates are historically important, but not commonly used today due to their slower onset of action, long recovery characteristics, and relatively small margin of safety. Pentobarbital is the prototypical oxybarbiturate. It has been combined with several adjunctive drugs for anesthesia. The thio (i.e., sulfur-substituted) analog of pentobarbital, thiopental, was commonly used in veterinary medicine for intravenous induction of anesthesia for many years but is no longer widley available.

Barbiturates cause anesthesia through global depression of CNS activity. This is accomplished through interference with nervous system impulse conduction. Like many other anesthetics, other excitable tissues can be affected, resulting in commonly encountered side effects, including depression of cardiorespiratory function. Barbiturates decrease cerebral blood flow (CBF) and the $CMRO_2$. $CMRO_2$ decreases progressively until electroencephalographic activity becomes isoelectric (Branson 2007).

Propofol

Propofol (2,6-di-isopropylphenol) is commonly used for sedation, induction, and maintenance of anesthesia in humans and domestic species. Propofol is supplied as a milky white liquid for intravenous injection. It is insoluble in aqueous solution therefore it is usually formulated as an emulsion of 10% soybean oil, 2.25% glycerol, and 1.2% egg phosphatide. Some formulations of propofol (e.g., Diprivan®, Propoflo™) do not contain preservative and will support bacterial and fungal growth should the drug become contaminated. This has led to the label recommendation of discarding unused drug at the end of the procedure or within 6 hours of opening a vial. Other formulations have additives such as benzyl alcohol (e.g., PropoFlo28®) to improve stability or reduce the potential of contamination with storage. Species-sensitivities to these additives should be investigated before their use (Davidson 2001).

Propofol is classified as an ultrashort-acting injectable anesthetic agent. Duration of effect is typically 5–10 minutes in dogs and 5–20 minutes in cats. Its rapid recovery characteristics are maintained in most species following prolonged infusions. Recovery times may be prolonged in the cat (and other species that have reduced capacity for glucuronidation of drugs) following repeated doses or continuous rate infusions.

Propofol has been used in dogs, cats, horses, pigs, goats, sheep, and even birds. Wild turkeys, mallard ducks, pigeons, and chickens have been anesthetized with propofol, but there is significant cardiorespiratory depression in ducks and chickens, indicating birds may need ventilatory support during anesthesia (Machin & Caulkett 1998). Apnea and respiratory depression are the best known side effects of propofol administration. The incidence of apnea may be reduced by administering the drug over 60–90 seconds (Muir & Gadawski 1998). It would be prudent to be prepared to intubate and support ventilation if apnea occurs. Pain is reported on propofol injection by some people. Muscle fasciculations and spontaneous twitching can occur in some animals.

Dissociative Anesthetics

Ketamine

Most veterinary formulations of ketamine are a racemic mixture consisting of two optical enantiomers. However, in many countries (*S*)-ketamine is available as a human or veterinary product. The *S* enantiomer is less cardiodepressant and has a four-fold greater affinity for the phencyclidine site in the NMDA receptor. Serotonin transport is inhibited two-fold by the *R* form. Some of ketamine's effects are not stereoselective. Norepinephrine release is equivalent from the *S* and *R* forms (Kohrs & Durieux 1998).

Ketamine can be administered intramuscularly to anesthetize animals which are not easily given drugs intravenously. Intramuscular administration will produce a longer duration of anesthesia than intravenous administration, but the recovery is usually longer and can be accompanied by more dysphoria. Recovery from ketamine appears to be due to redistribution and metabolism similar to the thiobarbiturates. Hepatic biotransformation to norketamine (metabolite I) and dehydronorketamine (metabolite II) is the major route of metabolism in most species studied. It was thought ketamine was excreted unchanged in the urine of cats, but this originated from one paper published in 1978 by Gaskell et al. and since that time it has been shown by Waterman that biotransformation is an important route of elimination in domestic cats (Waterman 1983). Norketamine is about one-third to one-fifth as potent as the parent compound but may contribute to the prolonged analgesic effects of ketamine (Kohrs & Durieux 1998).

Ketamine produces a form of anesthesia that is different from other hypnotic drugs. In general terms, ketamine induces anesthesia and amnesia by functional disruption (dissociation) of the CNS through marked CNS stimulation resulting in catalepsy, immobility, amnesia, and marked analgesia. Electroencephalographic analysis indicates that depression of the thalamoneocortical system occurs in conjunction with activation of the limbic system. Awakening from ketamine anesthesia in people is frequently characterized by disagreeable dreams and hallucinations. Sometimes these unpleasant occurrences may recur days or weeks later. Almost half of adults over the age of 30 exhibit delirium or excitement, or experience visual disturbances. The occurrence of adverse psychological experiences is much lower in children. The incidence of adverse psychological experiences in animals is unknown, but a significant number of animals transiently vocalize and have motor disturbances during recovery.

Ketamine's neuropharmacology is complex. The compound interacts with NMDA and non-NMDA glutamate receptors, nicotinic, muscarinic cholinergic, monoaminergic, and opioid receptors. In addition there are interactions with voltage-dependent ion channels such as Na^+ and L-type Ca^{2+} channels. It is believed that the NMDA receptor antagonism accounts for most of the analgesic, amnestic, psychomimetic, and neuroprotective effects of the compound, but the exact mechanism of its anesthetic action is not known. NMDA receptor activation is believed to play a role in the "memory" of the CNS, which is involved in the "wind-up," hyperalgesia, and allodynia seen in certain pain syndromes (Kohrs & Durieux 1998).

Ketamine can increase the $CMRO_2$ due to increased metabolic activity associated with increased activity in certain

areas of the brain. Intracranial pressure (ICP) also increases, possibly because of two mechanisms: (1) ketamine can increase mean arterial blood pressure so CBF can increase and ICP can passively increase in patients with altered autoregulation, and (2) ketamine can depress respiration, increasing the arterial partial pressure of carbon dioxide $PaCO_2$. The brain responds to elevations in $PaCO_2$ by increasing CBF, which will increase ICP. Ventilation may reduce the increase in CBF. Current clinical dogma dictates avoiding ketamine in patients with suspected head trauma.

Ketamine causes a characteristic breathing pattern termed *apneustic breathing*, characterized by prolonged inspiratory duration and relatively short expiratory time. When ketamine is administered by itself, it typically causes minimal respiratory depression that is short-lived. Hypoxic and hypercapnic respiratory regulation appears to remain intact, but ketamine is seldom given alone. It is often combined with benzodiazepines, acepromazine, opioids, or alpha-2 adrenergic agonists. The combined effect of these drugs is usually decreased minute ventilation, increased $PaCO_2$, and mild respiratory acidosis.

Ketamine, when given to animals with functioning sympathetic nervous systems, generally increases heart rate and arterial blood pressure. Cardiac output will usually stay the same or slightly increase. Ketamine is seldom given alone to healthy animals. The use of adjunctive drugs, such as benzodiazepines, acepromazine, or alpha-2 adrenergic agonists, tends to blunt the sympathomimetic effect of ketamine and will tend to decrease cardiac function and decrease arterial blood pressure.

Tiletamine/Zolazepam

Tiletamine/zolazepam combinations are available in a fixed ratio. Telazol® is a non-narcotic, nonbarbiturate, injectable anesthetic agent. Chemically, Telazol® is a combination of equal parts by weight of tiletamine hydrochloride (2-[ethylamino]-2-[2-thienyl]-cyclohexanone hydrochloride), an arylaminocycloalkanone dissociative anesthetic, and zolazepam hydrochloride (4-[o-fluorophenyl]-6,8-dihydro-1,3,8-trimethylpyazolo[3,4-e][1,4]diazepin-7[1H]-1-hydrochloride), a benzodiazepine having minor tranquilizing properties. The product is supplied sterile in vials, each containing a total of 500 mg of active drug as free base equivalents and 288.5 mg of mannitol. The addition of 5 mL of diluent produces a solution containing the equivalent of 50 mg of tiletamine base, 50 mg of zolazepam base and 57.7 mg of mannitol per milliliter. The resulting solution has a pH of 2–3.5. Zoletil® is available in many countries outside North America and is commonly marketed as a mixture containing 25 mg/mL each of zolazepam and tiletamine (Zoletil 50®) or 50 mg/mL each (Zoletil 100®).

Duration of effect is dependent on the route of administration and amount of drug given. When used intravenously it lasts approximately 15–20 minutes. When given intramuscularly it may last 30–45 minutes. It is commonly used in place of ketamine and its duration is typically longer.

Tiletamine induces dissociative anesthesia similar to ketamine. It has the potential to cause seizure activity, but when combined with zolazepam the incidence of seizures is greatly reduced. Its effects on CBF and ICP are similar to those of ketamine. Nephrotoxicity in New Zealand white rabbits has been reported following Telazol® administration (Doerning et al. 1992). Anecdotally, tigers do not appear to recover well after tiletamine/zolazepam therefore its use is generally contraindicated. Tiletamine/zolazepam can be combined with other drugs to improve its analgesic and recovery characteristics.

Miscellaneous Anesthetics

Etomidate

Etomidate has been used extensively as a hypnotic agent for the induction of anesthesia in humans, but less commonly in other species. Etomidate is a rapidly acting, ultrashort acting imidazole derivative. The duration of effect following intravenous bolus administration is typically 5–10 minutes. Etomidate causes dose-dependent CNS depression leading to sedation, hypnosis, and finally an isoelectric electroencephalogram.

Etomidate, in contrast to almost all other induction agents, does not seem to cause significant depression of cardiac contractility and has minimal effects on heart rate, cardiac output, and arterial blood pressure. Elimination of etomidate occurs by ester-hydrolysis in plasma and in the liver at approximately equal rates. Metabolism of etomidate in the liver is a capacity-limited Michaelis–Menten process. Hepatic hydrolysis results in the corresponding inactive carboxylic acid. Etomidate will temporarily reduce steroidogenesis (Boidin 1985; Moon 1997). Steroid synthesis usually increases with the stress of anesthesia so the net effect may be little or no change (Dodam et al. 1990). It is not a clinical contraindication except for animals with hypoadrenocorticism (Addison's disease). Intravenous administration of etomidate may induce excitement, myoclonus, pain on injection, vomiting, and apnea during induction of anesthesia. Some animals may have purposeless myoclonic muscle movements during recovery from anesthesia. The frequency and severity of the side effects can be attenuated or eliminated by the administration of adjunctive drugs such as diazepam, acepromazine, or opioids prior to etomidate administration. A constant rate infusion of etomidate may result in hemolysis (Van de Wiele et al. 1995; Moon 1994). This is thought to be due to

the propylene glycol carrier and the very high osmolality of available products (Doenicke et al. 1997).

Alfaxalone

Alfaxan®

Alfaxalone is a synthetic neurosteroid anesthetic with a relatively wide margin of safety and little cardiovascular or respiratory depression. Due to its poor water solubility, earlier formulations (Saffan®) were a mixture of alfaxalone and alfadolone combined with cremophor EL® as a solubilizing agent. Adverse effects, including histamine release and anaphylactic reactions associated with Cremophor, led to the withdrawal of that product from the market. A novel formulation of alfaxalone, Alfaxan-CD®, was released in Australia in 2001, in the United Kindgom in 2007, in Europe in 2008, in Canada in 2011, and in the United States in 2012. It is a 1% aqueous solution with a pH of 6.5–7.0 containing a non-cremophor vehicle (2-hydroxypropyl-β-cyclodextrin) which does not cause histamine release. The drug is approved for induction and maintenance of general anesthesia in dogs and cats via intravenous administration and has also been approved for intramuscular administration in some countries. Until recently, Alfaxan® was exclusively supplied as a 10-mL vial without added antimicrobial preservatives. This resulted in a shelf-life of only 6 hours and a label recommendation to discard unused drug within this timeframe (Berry 2015). A newer multidose formulation containing the preservatives ethanol, chlorocresol, and benzethonium chloride has recently been approved and appears to have the same efficacy and safety as the preservative-free formulation but offers the advantage of a 28-day shelf-life.

Like other injectable anesthetics, alfaxalone produces its clinical effects via potentiation of GABA at $GABA_A$ receptors in the CNS, resulting in modulation of chloride transport and neuronal hyperpolarization (Berry 2015). After intravenous administration, it produces rapid onset of action and satisfactory muscle relaxation but has no significant analgesic effects. In dogs and cats, it undergoes rapid hepatic metabolism, has a relatively short half-life, and does not accumulate after repeated dosing (Ambros et al. 2008; Ferre et al. 2006; Whittem et al. 2008).

Depending on the species and country-specific labelling, alfaxalone can be used for intramuscular sedation or premedication, for intravenous induction of anesthesia prior to transfer to an inhaled agent, or for intravenous maintenance of anesthesia via intermittent boluses for short procedures or via continuous rate infusion (CRI) for longer procedures. Other off-label routes of administration have been reported, including subcutaneous injection in various domestic and exotic species, intraperitoneal injection in laboratory animals, and immersion/irrigation in fish and amphibians.

Premedication or coadministration with a sedative and/or analgesic is recommended to reduce the dose of alfaxalone required, provide analgesia, and smooth recovery, which can otherwise be rough. Paddling, vocalization, rigidity, myoclonus, and trembling have been reported in dogs and cats recovering from alfaxalone that did not receive other drugs concurrently (Berry 2015). Also, with intramuscular administration, the relatively large volume of alfaxalone required can be a limiting factor and coadministration of more potent sedative and/or analgesic agents may help overcome this.

Alfaxalone produces dose-dependent respiratory depression and apnea is common after rapid intravenous injection of clinically relevant doses (Muir et al. 2008, 2009). Slow injection over 60 seconds is recommended and the anesthetist should be prepared to intubate, provide supplemental oxygen, and support ventilation when administering alfaxalone. Cardiac output and arterial blood pressure remain generally stable after administration of clinically appropriate doses in healthy patients, although caution should be exercised when administering alfaxalone to patients with limited cardiac reserve capacity or hemodynamic instability.

In addition to dogs and cats, off-label alfaxalone use has been reported in many other domestic species and exotic pets, including horses, sheep, swine, rabbits, ferrets, rodents (excluding mice, rats, guinea pigs, chinchillas), birds (excluding budgerigars and finches), reptiles (excluding lizards, turtles, tortoises, and snakes), and amphibians (excluding frogs, toads, and axolotls). It has also been used in a diverse range of captive zoo species (excluding civet cats, macaques, sea lions, crocodiles, pythons, flamingos, parrots, blue crabs, carp, and tarantulas); as well as in free-ranging wildlife (excluding deer, bighorn sheep, seals, koalas, wallabies, and river turtles).

Opioids

All drugs classified as opioids are chemically related to a group of compounds which have been purified from the juice of a particular species of poppy, *Papaverum somniferum*. The unrefined extract from the poppy is called opium and contains approximately 20 naturally occurring pharmacologically active compounds, including morphine and codeine. In addition, numerous semisynthetic and synthetic analogs of these natural compounds have been developed for clinical use. The word "opioid" is typically used to encompass all chemical derivatives of the compounds purified from opium and will be the term used to describe this class of analgesics throughout this section.