ZOO ANIMAL AND WILDLIFE IMMOBILIZATION AND ANESTHESIA

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Section I
General

1 Clinical Pharmacology

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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 (PK) can be generally defined as what an organism does to a drug. Absorption, distribution, biotransformation, and elimination are processes that determine the concentration of the 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 (PD) can be generally defined as what a drug does to an organism. PD 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. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production by binding to cyclooxygenase enzyme isoforms. Relating plasma drug concentrations to observed NSAIDs actions can be complex in comparison with other drugs (e.g., opioids) due to the different nature of their action. Preexisting progstaglandins, as well as their slower process of inhibiting an enzyme system, confound the relationship between drug concentration and effect. The molecular actions of inhalant anesthetics have not been completely characterized, even though their clinical use has been well described (Steffey & Mama 2007).

Pharmacodynamic effects are predictable for most clinically used drugs. However, individual animal

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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 that 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 are able to 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).

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

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

Source: Adapted from Steffey EP, Mama RM. 2007. Inhalation anesthetics. In: *Lumb and Jones' Veterinary Anesthesia*, 4th ed. (WJ Tranquilli, JT Thurmon, KA Grimm, eds.). Ames: Blackwell.

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 CNS depression correlates directly with the partial pressure of isoflurane within the brain) (see Table 1.1) (Steffey & Mama 2007).

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 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.

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.

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	1.4	1.4
Sevoflurane	0.69	1.7
Methoxyflurane	12.0	2.0
Isoflurane	2.6	2.7
Halothane	2.9	2.9

Source: Adapted from Steffey EP, Mama RM. 2007. Inhalation anesthetics. In: *Lumb and Jones' Veterinary Anesthesia*, 4th ed. (WJ Tranquilli, JT Thurmon, KA Grimm, eds.). Ames: Blackwell.

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 following 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 & Mama 2007). Partition coefficients are not absolute constants for an anesthetic agent. Tissue composition may change as a function of age, sex, body condition, and so on, and these changes may influence partitioning.

Mechanism of Action of Inhaled Anesthetics The specific mechanism of action of most anesthetics remains unknown. Volatile anesthetics appear to share some common cellular actions with other sedative, hypnotic, or analgesic drugs. A sound theory of anesthetic action should provide an explanation for the observed correlation of potency with the oil/gas partition coefficient, the observation that a large number of diverse chemical structures can cause anesthesia, and explain why the agents produce side effects. Experimental work has implicated a protein "target" on a diverse population of ionophores that is required for anesthetic action (Franks & Lieb 2004). The alteration in ionophore conductance may be related to direct action of the anesthetic at a two amino acid sequence within the transmembrane spanning domains.

The protein receptor hypothesis postulates that protein receptors in the central nervous system are responsible for the mechanism of action of inhaled anesthetics. This theory is supported by the steep dose–response curve for inhaled anesthetics. However, it remains unclear if inhaled agents disrupt ion flow through membrane channels by an indirect action on the lipid membrane, via a second messenger, or by direct and specific binding to channel proteins. Another theory describes the activation of gamma-aminobutyric acid (GABA) receptors by the inhalation anesthetics. Volatile agents may activate or facilitate GABA channels, resulting in hyperpolarized cell membranes. In addition, they may inhibit certain calcium channels, preventing the release of neurotransmitters and inhibit glutamate channels.

Evidence for the protein receptor theory includes the observation made by Franks and Lieb that a broad range of inhalant anesthetics inhibited the water-soluble enzyme firefly luciferase (Franks & Lieb 1984). This enzyme hydrolyzes luciferin to create light and is often a model for anesthetic action because the rank orders of potency of the anesthetics in animals parallels that of luciferase inhibition. Franks and Lieb studied the enzyme in a lipid free environment, with only the enzyme present, and observed the enzyme could be completely inhibited. This suggests the site of action is within the protein structure and is not strictly dependent on lipid. Franks and Lieb also noted that some anesthetics exist as stereoisomers and that the effects of these isomers can differ. However, when the stereoisomers are introduced into a lipid substrate, the physical effects on the lipid are identical. This is further evidence that the anesthetic is acting at a stereoselective "receptor" and would implicate a protein as the site of action.

Following up on the work by Franks and Lieb, Harrison, Harris, Mihic, and colleagues attempted to reconcile the apparent problem of the nonspecific action of anesthetics on a wide range of protein channels including glycine, glutamate, GABA, and other neurotransmitter activated channels (Mihic et al. 1997). For the anesthetic to act on all of these channels, one would expect a target amino acid sequence would be conserved among all channels or the anesthetic would be altering receptor function by distorting the surrounding environment. In their experiments, this group began making chimeric DNA encoding the c-terminal human GABA rho receptor subunit, which is an anesthetic insensitive receptor, and the N-terminal glycine-binding part of the human glycine alpha-receptor subunit that is situated in the transmembrane spanning domain. They expressed the cDNA in *Xenopus* oocytes and measured resulting chloride conductance. They determined the site of anesthetic action was within the N-terminal sequence of the third transmembrane spanning domain. The researchers then began to construct cDNA containing point mutations within this region and created receptors that were insensitive

to enflurane. They ultimately found two amino acids in the glycine receptor that abolished enflurane sensitivity when mutated. Changing the corresponding amino acids on the GABA receptor also abolished enflurane sensitivity. However, these mutations did not reduce the receptor's sensitivity to the injectable anesthetic propofol.

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 1.4 (Steffey & Mama 2007). This means that if the gas partial pressures are in equilibrium, the concentration in blood will be 1.4 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 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 & Mama 2007). 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 does not 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; however, 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 is 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.

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 & Mama 2007). 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), 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 ventila-

tion 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, 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 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 a piece of cotton soaked with agent held near the nose (not recommended), or can be as complex as the Tec 6 vaporizer for desflurane.

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 (OSHA) 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 recommendations offered by the National Institute of Occupational Safety and Health (NIOSH). The NIOSH recommends that the maximum time-weighted average concentration of volatile halogenated anesthetics should not exceed 2 ppm when used alone or 0.5 ppm when used with nitrous oxide, and that nitrous oxide concentration should not exceed 25 ppm (American College of Veterinary Anesthesiologists 1996).

Minimum Alveolar Concentration (MAC)

The measurement of the dose of an inhalant anesthetic is the minimum alveolar concentration (MAC) multiple. It is defined as the minimum alveolar concentration at 1 atm, required to prevent gross purposeful movement in 50% of the subjects tested, following a 60-second application of a supramaximal stimulus (Steffey & Mama 2007). One MAC is by definition the EC_{50} (i.e., 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 α_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 central nervous system. 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 $CMRO_2$ (Algotsson et al. 1992; Hoffman et al. 1995; Roald et al. 1991). Halothane is also a poor choice because of its significant effects on cerebral blood flow autoregulation (Steffey & Mama 2007). Isoflurane, sevoflurane, and desflurane are the inhalants of choice at this time.

Cardiovascular System Most inhalant anesthetic agents cause direct myocardial depression. Halothane is the most depressant on contractility; however, it generally has the fewest effects on vascular resistance (Steffey & Mama 2007). 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; however, 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 upon 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 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 a 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 & Mama 2007). 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 & Mama 2007). Commercially available halothane contains thymol, a preservative, that 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. Isoflurane 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 & Mama 2007). 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 (VOC) should be used to deliver the agent. However, several reports of the use of modified 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. Administration of fluids and/or sympathomimetic agents can usually counteract the observed hypotension. Likewise, administering preanesthetic drugs (e.g., opioids) that reduce the amount of inhalant required will also reduce the degree of vasodilation.

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 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 & Mama 2007). Desflurane boils at 23°C and must be handled using a 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) that 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 & Mama 2007). This fluoride exposure doesnot 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 non-irritating 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 min. 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 is available (Table 1.3).

Table 1.3. Structure and characteristics of inhalation anesthetics

Agent	Year Introduced	Structure	Type
Halothane	1956	CF3–CHClBr	Alkane
Isoflurane	1981	CF3CHCl–O–CHF2	Ether
Enflurane	1972	CHClF–CF2–O–CHF2	Ether
Methoxyflurane	1960	CHCl2–CF2–O–CH3	Ether
Desflurane	1992	CF3CHF–O–CHF2	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 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 protypical oxybarbiturate. It has been combined with several adjunctive drugs for anesthesia. The thio (i.e., sulfur substituted) analog of pentobarbital, thiopental, is still used by intravenous administration for induction of anesthesia in domestic animals. However, perivascular injection can result in tissue necrosis, and its use in nondomestic species is limited due to the inability to obtain reliable intravenous access prior to anesthetic induction and current availability problems.

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 cerebral metabolic requirement for oxygen ($CMRO_2$). Cerebral metabolic requirement for oxygen decreases progressively until electroencephalographic activity becomes isoelectric (Branson 2007).

Propofol

Propofol (2,6-diisopropylphenol) 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. A newer formulation has been available in some European contries (PropoClear®) which uses a different carrier solution than the traditional soybean emulsion. The inhibition of bacterial growth allowed a 28-day shelf life. However, there have been reports of tissue irritation following injection, and the product is being reevalutaed. Some 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 fourfold greater affinity for the phencyclidine site in the NMDA (N-methyl-D-aspartate) receptor. Serotonin transport is inhibited twofold 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 (a.k.a. metabolite I) and dehydronorketamine (aka metabolite II) is the major route of metabolism in most species studied. It was thought ketamine was excreted unchanged in the urine of cats, however 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 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; however, a significant number of animals transiently vocalize and have motor disturbances during recovery.

Ketamine's neuropharmacology is complex. The compound interacts with N-methyl-D-aspartate 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 central nervous system, 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 cerebral blood flow (CBF) can increase and ICP passively increase in patients with altered autoregulation, and (2) Ketamine can depress respiration increasing P_aCO_2. The brain responds to elevations in P_aCO_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. Howevere, 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 P_aCO_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/zolazapam combinations are available in a fixed ratio. Telazol® is a nonnarcotic, 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 mannitol. The addition of 5-mL diluent produces a solution containing the equivalent of 50-mg tiletamine base, 50-mg zolazepam base, and 57.7-mg 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 upon 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; however 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 man, 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 adjunctive drugs, such as diazepam, acepromazine, or opioids prior to etomidate administration. A constant rate infusion of etomidate may result in hemolysis (Moon 1994; Van de Wiele et al. 1995). This is thought to be due to the propylene glycol carrier and the very high osmolality of available products (Doenicke et al. 1997).

Alphaxalone/Alphadolone

Saffan® Alphaxalone is a steroid anesthetic with a relatively wide margin of safety, little cardiovascular or respiratory depression, and minimal induction and recovery excitement. Alphaxalone is poorly soluble in water so to improve solubility, it is formulated with another steroid, alphadolone acetate, which also has anesthetic activity. The addition of alphadolone increases the water solubility of alphaxalone by threefold. One commercially available formulation, Saffan®, is a mixture of alphadolone, alphaxalone, and cremophor EL®. The cremophor is a nonionic surfactant, which makes the aqueous solution possible; however, cremaphor can cause histamine release and severe cardiovascular adverse events in some species (e.g., domestic dog). The main route of elimination is by biotransformation in the liver and secretion in the bile.

Alfaxan CD® Alphaxalone is available as a novel formulation that uses cyclodextran in water as a solvent rather than cremophor EL. The resulting compound lacks the histamine-releasing properties of Saffan, yet retains the therapeutic index and efficacy of alphaxalone.

OPIOIDS

All drugs classified as "opioids" are chemically related to a group of compounds that 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.

The opioids are a versatile group of drugs with extensive applications related to the management of pain in companion animal veterinary medicine. In the past, their use in wild and exotic species has been largely limited to the ultra-potent agents utilized in remote capture techniques. However, with the rapid evolution of zoo animal medicine and surgery, the opioids are being used increasingly as analgesics for the management of surgical pain in a wide variety of species. Though there are few pharmacokinetic or pharmacodynamic studies involving opioids in wild and exotic animals, a general discussion of opioid pharmacology is relevant and may facilitate extrapolation from companion animal species.

Opioid Receptors

It is well known that exogenously administered opioids, such as morphine or heroin, exert their effects by interacting with specific opioid receptors and mimicking naturally occurring molecules known as endogenous opioid peptides. Based on work carried out over the past 20 years, it is now accepted that there are three well-defined types of opioid receptors, most commonly known by their Greek letter designations as μ (mu), δ (delta), and κ (kappa) (Harrison et al. 1998; Inturrisi 2002; Janecka et al. 2004; Kieffer 1999). This classic system of nomenclature has been under reconsideration for a number of years and during this time several alternative naming systems have been proposed leading to considerable confusion. In addition, a fourth type of opioid receptor, the nociceptin receptor (also known as the orphanin FQ receptor) has been characterized (Moran et al. 2000; Smith & Moran 2001). According to the most recent recommendations of the International Union of Pharmacology subcommittee on nomenclature, variations based on the Greek letters remain acceptable. Thus, mu, μ or MOP (for "mu opioid peptide"); delta, δ or DOP (for "delta opioid peptide"); kappa, κ or KOP (for "kappa opioid peptide"); and NOP (for "nociceptin opioid peptide") are considered interchangeable abbreviations. Distinct cDNA sequences have been cloned for all four opioid receptor types, and each type appears to have a unique distribution in the brain, spinal cord, and periphery (Smith & Lee 2003).

The diversity of opioid receptors is further extended by the existence of several subtypes of μ, δ, and κ receptors. Based on pharmacologic studies, there are thought to be at least three μ receptor subtypes, μ_1, μ_2, and μ_3; two δ receptor subtypes, δ_1, and δ_2; and perhaps as many as four κ receptor subtypes, κ_{1a}, κ_{1b}, κ_2, and κ_3 (Smith & Lee 2003). The discovery of opioid receptor subtypes generated great enthusiasm among researchers and introduced the possibility of developing subtype-specific therapeutic agents with favorable side effect profiles. At this point, however, the functional significance of these receptor subtypes remains unclear,

and distinct cDNA sequences corresponding to these subtypes have not yet been identified (Smith & Lee 2003).

In general, it appears that the μ receptor mediates most of the clinically relevant analgesic effects, as well as most of the adverse side effects associated with opioid administration (Kieffer 1999). Drugs acting at the δ receptor tend to be poor analgesics, but may modify μ receptor-mediated antinociception under certain circumstances and mediate opioid receptor "cross-talk." The κ receptor mediates analgesia in several specific locations in the central nervous system and the periphery; however, distinguishing μ- and κ-mediated analgesic effects has proven to be difficult (Kieffer 1999; Smith & Lee 2003). In contrast to the classic opioid receptors, the nociceptin receptor does not mediate typical opioid analgesia, but instead produces antiopioid (pronociceptive) effects (Inturrisi 2002; Janecka et al. 2004; Moran et al. 2000; Smith & Moran 2001). Due to the considerable structural homology between the three classically described opioid receptors, it is likely that there are significant interactions between these receptors in different tissues, and the loosely defined physiologic roles ascribed to each receptor type still require further clarification.

Endogenous Opioid Receptor Ligands

The opioid receptors discussed earlier are part of an extensive opioid system that includes a large number of endogenous opioid peptide ligands. Endogenous opioid peptides are small molecules that are naturally produced in the central nervous system and in various glands throughout the body, such as the pituitary and the adrenal (Janecka et al. 2004). Three classical families of endogenous opioid peptides have been identified: the enkephalins, the dynorphins, and β-endorphin. Each of these is derived from a distinct precursor polypeptide, pro-enkephalin, pro-dynorphin, and pro-opiomelanocortin, respectively (Janecka et al. 2004). These classical endogenous opioid peptides are expressed throughout the central nervous system, and their presence has more recently been confirmed in peripheral tissues as well (Janecka et al. 2004). There are considerable structural similarities between these three groups of peptides, and each family demonstrates variable affinities for μ, δ, and κ receptors. None of them bind exclusively to a single opioid receptor and none of them have any significant affinity for the nociceptin receptor. The physiological roles of these peptides are not completely understood at this time. They appear to function as neurotransmitters, neuromodulators and, in some cases, as neurohormones. They mediate some forms of stress-induced analgesia and also play a role in analgesia induced by electrical stimulation of discrete regions in the brain, such as the periaqueductal gray of the mesencephalon (Inturrisi 2002).

Nociceptin (also known as orphanin FQ) is the endogenous ligand for the more recently discovered nociceptin receptor. Nociceptin is derived from pronociceptin, and its amino acid sequence is closely related to that of the classical endogenous opioid peptides discussed earlier (Janecka et al. 2004; Moran et al. 2000). Despite this homology, nociceptin binding is specific for the nociceptin-receptor and the peptide does not appear to interact with μ, δ, or κ receptors. Furthermore, the physiologic effects of nociceptin are in direct contrast to the actions of the classical endogenous opioid peptides, with nociceptin producing a distinctly pro-nociceptive effect (Janecka et al. 2004; Moran et al. 2000; Smith & Moran 2001). The functional significance of nociceptin and its receptor remain to be elucidated, but additional insight into this novel opioid peptide may have substantial implications in future therapeutic drug development.

In addition to the enkephalins, dynorphins, β-endorphin, and nociceptin, there are now two other recently discovered endogenous opioid peptides called endomorphin-1 and endomorphin-2 (Zadina et al. 1999). These peptides are putative products of an, as yet, unidentified precursor, and have been proposed to be the highly selective endogenous ligands for the μ receptor (Janecka et al. 2004; Zadina et al. 1999). The endomorphins are small tetrapeptides that are structurally unrelated to the classical endogenous opioid peptides (Zadina et al. 1999). Their identification has heralded a new era in research of the μ opioid system, which may contribute to our understanding of the neurobiology of opioids, and provide new avenues for therapeutic interventions.

Opioid Receptor Signaling and Mechanisms of Analgesia

Binding of an opioid agonist to a neuronal opioid receptor, regardless of whether the agonist is endogenous or exogenous, typically leads to several events that serve to inhibit the activation of the neuron. Opioid receptors are part of a large superfamily of membrane-bound receptors that are coupled to G-proteins (Smith & Lee 2003). As such, they are structurally and functionally related to receptors for many neurotransmitters and other neuropeptides ,which act to modulate the activity of nerve cells. Opioid receptor binding, via activation of various types of G-proteins, may lead to inhibition of adenylyl cyclase (cAMP) activity, activation of receptor-operated K^+ currents, and suppression of voltage-gated Ca^{2+} currents (Inturrisi 2002).

At the presynaptic level, decreased Ca^{2+} influx will result in reduced release of transmitter substances, such as substance P, from primary afferent fibers in the spinal cord dorsal horn, thereby inhibiting synaptic transmission of nociceptive input (Inturrisi 2002). Postsynaptically, enhanced K^+ efflux will result in

neuronal hyperpolarization of spinal cord projection neurons and inhibition of ascending nociceptive pathways. A third potential mode of opioid action involves upregulation of supraspinal descending antinociceptive pathways in the periaqueductal gray. It is now known that this system is subject to tonic inhibition mediated by GABAergic neurons, and opioid receptor activation has been shown to suppress this inhibitory influence and augment descending antinociceptive transmission (Christie et al. 2000; Inturrisi 2002). The proposed cellular basis for this involves μ receptors present on presynaptic GABAergic nerve terminals, which activate voltage-dependent K^+ currents and thereby inhibit GABA release into the synaptic cleft (Christie et al. 2000). It is important to note that while our collective understanding of opioid receptor-mediated signaling has increased dramatically in recent years, the relationship of such subcellular events to clinical analgesia at the level of the organism requires further clarification.

Opioid Receptor Distribution and Therapeutic Implications

While cellular and molecular studies of opioid receptors and ligands are invaluable in understanding their function, it is critical to place them in their anatomical and physiological context to fully appreciate the opioid system and its relevance to pain management. It has long been a principle tenet of opioid analgesia that these agents are centrally acting, and this understanding has shaped the way we use opioid analgesics clinically. It has been well established that the analgesic effects of opioids arise from their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn, and to activate pain control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord. Within the central nervous system, evidence of μ, δ, and κ opioid receptor mRNA and/or opioid peptide binding has been demonstrated in supraspinal sites including the mesencephalic periaqueductal gray, the mesencephalic reticular formation, various nuclei of the rostral ventromedial medulla, forebrain regions including the nucleus accumbens, as well as spinally within the dorsal horn (Gutstein & Akil 2001; Yaksh 1998). The interactions between groups of opioid receptors at various spinal and supraspinal locations, as well as interactions between different receptor types within a given location, are complex and incompletely understood at this time.

Systemic administration of opioid analgesics via intravenous, intramuscular, or subcutaneous injection will result in a relatively rapid onset of action via interaction with these central nervous system receptors. Oral, transdermal, rectal, or buccal mucosal administration of opioids will result in variable systemic absorption, depending on the characteristics of the particular agent, with analgesic effects being mediated largely by the same receptors within the central nervous system. In addition, neuraxial administration, either into the subarachnoid or epidural space, is a particularly efficacious route of administration. Small doses of opioids introduced via these routes readily penetrate the spinal cord and interact with spinal and/or supraspinal opioid receptors to produce profound and potentially long-lasting analgesia, the characteristics of which will depend on the particular drug utilized.

Despite the fact that opioids have long been considered the prototype of centrally acting analgesics, a body of evidence has emerged over the past decade, which clearly indicates that opioids can produce potent and clinically measurable analgesia by activation of opioid receptors in the peripheral nervous system (Stein et al. 2001). Opioid receptors of all three major types have been identified on the processes of sensory neurons, and they respond to peripherally applied opioids and locally released endogenous opioid peptides when upregulated during inflammatory pain states (Fields et al. 1980; Stein 1993; Stein et al. 1993, 2001, 2003). Furthermore, sympathetic neurons and immune cells have also been shown to express opioid receptors, but their functional role remains unclear (Stein et al. 2003). While the binding characteristics of peripheral and central opioid receptors are similar, the molecular mass of peripheral and central μ opioid receptors appears to be different, suggesting that selective ligands for these peripheral receptors could be developed, which would produce opioid analgesia without the potential to induce centrally mediated adverse side effects (Stein 1995; Stein & Yassouridis 1997; Stein et al. 1996, 2001, 2003).

Adverse Effects of Clinically Used Opioids

While opioids are used clinically primarily for their pain relieving properties, they also produce a host of other effects on a variety of body systems. This is not surprising in light of the wide distribution of endogenous opioid peptides and their receptors in supraspinal, spinal and peripheral locations. Since information regarding opioid side effects in most wild and exotic animals is lacking, reference is made to common domestic species, where appropriate.

Central Nervous System

Level of Arousal There are considerable species differences in the central nervous system response to opioid analgesics that cannot be attributed to pharmacokinetic variations alone. Central nervous system depression (i.e., sedation) is typically seen in the dog, monkey, and human, while central nervous system stimulation (i.e., excitement and/or spontaneous locomotor activity) may be elicited in the cat, horse, goat, sheep, pig, and cow following systemic administration of various opioids, most notably morphine (Branson et al. 2001).

Reasons for these different responses are not entirely clear at this time, but are presumably related to differing concentrations and distributions of μ, δ, and κ receptors in various regions of the brain in these species (Hellyer et al. 2003). Details regarding the central nervous system responses of specific wild and exotic species to opioids are not known at this time. Regardless of the species, however, there are numerous factors which may play a role, including the temperament or condition of the animal, the presence or absence of pain in the animal, the dose, route and timing of drug administration, and the specific opioid administered.

Thermoregulatory Center The hypothalamic thermoregulatory system is also affected by opioid administration. Hypothermia tends to be the most common response, particularly when opioids are used during the perioperative period in the presence of other central nervous system depressant drugs (Branson et al. 2001; Gutstein & Akil 2001). Under some clinical circumstances, however, hyperthermia is observed in cats, horses, swine, and ruminants following opioid administration (Niedfeldt & Robertson 2006; Posner et al. 2007, 2010). Part of this increase in body temperature may be attributed to an increase in muscle activity associated with central nervous system excitation in these species; however, a specific central hypothalamic mechanism has also been implicated but remains poorly understood (Branson et al. 2001).

Emetic Center Nausea and vomiting associated with opioid administration are a result of direct stimulation of the chemoreceptor trigger zone for emesis located in the area postrema of the medulla (Gutstein & Akil 2001; Stoelting 1999). As with the other centrally mediated side effects, species plays a role in determining an individual's tendency to vomit after an opioid is administered. Horses, rabbits, ruminants, and swine do not vomit with opioid administration. Cats may vomit, but usually at doses that are greater than those which stimulate vomiting in dogs. Dogs will commonly vomit following opioid administration, especially with morphine.

Cough Center Opioids have variable efficacy in depressing the cough reflex, at least in part by a direct effect on a cough center located in the medulla (Gutstein & Akil 2001). Certain opioids are more effective antitussives than others, including drugs such as codeine, hydrocodone, and butorphanol.

Pupillary Diameter As a general rule, opioids tend to produce mydriasis in those species that exhibit central nervous system excitation, and miosis in those that become sedated following opioid administration (Branson et al. 2001; Stephan et al. 2003; Lee & Wang 1975; Wallenstein & Wang 1979). Miosis is due to an excitatory action of opioids on neuronal firing in the oculomotor nucleus (Lee & Wang 1975; Stoelting 1999; Wallenstein & Wang 1979). In the cat, and presumably in other species that exhibit mydriasis, this increase in activity in the oculomotor nuclear complex still occurs, but the miotic effect is masked by increased release of catecholamines, which results in mydriasis (Wallenstein & Wang 1979).

Respiratory System Opioids produce dose-dependent depression of ventilation, primarily mediated by μ_2 receptors leading to a direct depressant effect on brainstem respiratory centers (Gutstein & Akil 2001; Stoelting 1999). This effect is characterized by decreased responsiveness of these centers to carbon dioxide and is reflected in an increased resting $PaCO_2$ and displacement of the carbon dioxide response curve to the right. This effect is compounded by the coadministration of sedative and/or anesthetic agents, meaning that significant respiratory depression and hypercapnia are much more likely to occur in anesthetized patients that receive opioids versus those that are conscious. It should be noted that, in general, humans tend to be more sensitive to the respiratory depressant effects of opioids when compared with most veterinary species. However, respiratory support and/or specific opioid antagonists should be immediately available anytime very high doses, or very potent opioids, are used.

Cardiovascular System Most opioids have minimal effects on cardiac output, cardiac rhythm, and arterial blood pressure when clinically relevant analgesic doses are administered. Bradycardia may occur as a result of opioid-induced medullary vagal stimulation and will respond readily to anticholinergic treatment if warranted. Particular opioids (morphine and merperidine) can cause release of histamine, especially after rapid intravenous administration, which may lead to vasodilation and hypotension (Branson et al. 2001; Smith et al. 2001). Due to their relatively benign effects on cardiovascular function, opioids commonly form the basis of anesthetic protocols for human patients or animals with preexisting cardiovascular disease.

Gastrointestinal System The gastrointestinal effects of the opioids are mediated by μ and δ receptors located in the myenteric plexus of the gastrointestinal tract (Branson et al. 2001; Gutstein & Akil 2001). Opioid administration may stimulate defecation in certain species. Following this initial response, spasm of gastrointestinal smooth muscle predisposes to ileus and constipation. Horses and ruminants in particular may be predisposed to gastrointestinal complications associated with opioid administration, such as colic and ruminal tympany, respectively. Chronic opioid use may predispose to gastrointestinal stasis in other species.

In human patients, opioids (most notably fentanyl and morphine) have been shown to increase bile duct pressure through constriction of the sphincter of Oddi (Radnay et al. 1984). The incidence of this side effect in humans is, however, quite low (Jones et al. 1981). The incidence of increased bile duct pressure secondary to opioid administration in various animal species, and its potential clinical significance, is unknown at this time.

Genitourinary System Opioids, particularly when administered neuraxially, may cause urinary retention through dose-dependent suppression of detrusor contractility and decreased sensation of urge (el Bindary & Abu el-Nasr 2001; Kuipers et al. 2004). Urine volume may also be affected by opioids, and the mechanism of this effect appears to be multifactorial. Mu agonists tend to produce oliguria in the clinical setting, and this is in part a result of increased antidiuretic hormone release, leading to altered renal tubular function (Mercadante & Arcuri 2004; Stoelting 1999). Elevations in circulating plasma atrial natriuretic peptide may also play a role in morphine-induced antidiuresis (Mercadante & Arcuri 2004). Conversely, κ agonists tend to produce a diuretic effect, possibly through inhibition of antidiuretic hormone secretion (Mercadante & Arcuri 2004; Stoelting 1999). Other peripheral mechanisms involving stimulation of renal alpha-2 adrenergic receptors may also contribute to this κ agonist effect (Mercadante & Arcuri 2004).

Opioid Agonists

Almost all clinically useful opioids exert their analgesic and immobilizing effects by acting as agonists at μ receptors. While there are a few opioids that act as κ agonists, these drugs also tend to have antagonist or partial agonist effects at μ and/or δ receptors and are thus not classified as *pure* agonists. Pure or full opioid agonists are capable of eliciting maximal activation of the receptor when they bind it and the subsequent downstream processes result in a maximal analgesic effect (Fig. 1.1). Clinically, the full μ agonists are superior analgesics, and they are the drugs of choice for pain of moderate to severe intensity in many veterinary species. The following section contains brief descriptions of full μ agonists currently used in veterinary medicine. Specific details regarding μ agonist clinical pharmacology in various wild and exotic species is lacking.

Morphine (Morphine Sulfate) Morphine is the prototypical opioid analgesic and acts as a full agonist not only at μ receptors, but also at δ and κ receptors (Gutstein & Akil 2001). Despite the development of numerous synthetic opioids, many of which are more potent than morphine and may have other characteristics that make them desirable alternatives to morphine in

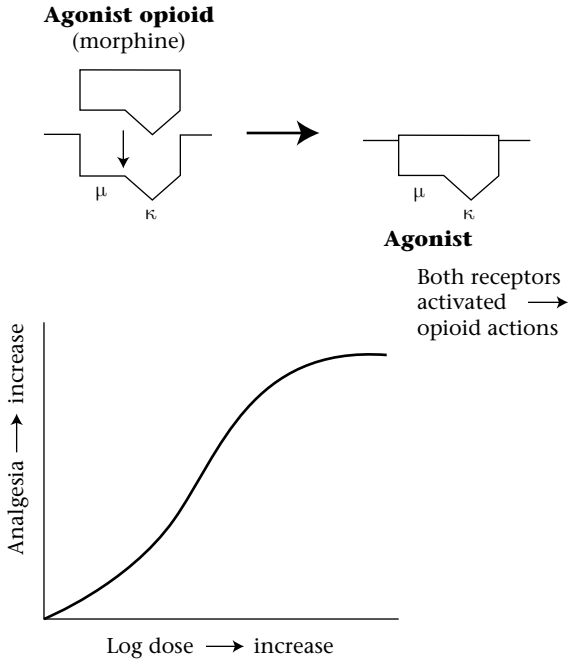

Figure 1.1. Effects of opioid agonists.

certain circumstances, it is worth noting that no other drug has been shown to be more efficacious than morphine at relieving pain in humans. Compared with the synthetic opioid agonists, morphine is relatively hydrophilic in nature and crosses the blood–brain barrier more slowly than fentanyl or oxymorphone, thereby delaying the peak effect somewhat even after intravenous administration (Gutstein & Akil 2001; Stoelting 1999). Clinically, this lag is not likely to be significant under most circumstances, with the onset of analgesia occurring reasonably promptly after a single dose of morphine and typically lasting 3–4 hours (Barnhart et al. 2000; Taylor et al. 2001). Morphine's poor lipid solubility means that it can produce long-lasting analgesia when administered into the epidural or subarachnoid space, with effects persisting for 12–24 hours. The first-pass effect is significant after oral administration and the bioavailability of oral morphine preparations is only in the range of 25%.

In most species, the primary metabolic pathway for morphine involves conjugation with glucuronic acid leading to the formation of two major metabolites, morphine-6-glucuronide and morphine-3-glucuronide (Faura et al. 1998; Gutstein & Akil 2001). Despite the low levels of glucuronyl transferase in the cat, the PK of morphine in this species seem to be broadly comparable with the dog and human, though clearance rates may be marginally slower (Barnhart et al. 2000; Faura et al. 1998; Taylor et al. 2001). This suggests that morphine must undergo a different type of conjugation reaction in this species. Morphine-6-glucuronide has pharmacological activities that are indistinguishable

from those of morphine in animal models and in human beings, while morphine-3-glucuronide appears to have little affinity for opioid receptors, but may contribute to the excitatory effects of morphine in some situations (Gutstein & Akil 2001; Smith 2000). With chronic morphine administration, it is likely that the active metabolite, morphine-6-glucuronide, contributes significantly to clinical analgesia.

Very little morphine is excreted unchanged in the urine. The major metabolites, morphine-3-glucuronide and, to a lesser extent, morphine-6-glucuronide, are eliminated almost entirely via glomerular filtration. In human patients, renal failure may lead to accumulation of morphine-6-glucuronide and persistent clinical effects, while liver dysfunction seems to have minimal impact on morphine clearance (Gutstein & Akil 2001; Stoelting 1999).

The side effects associated with morphine administration are typical of most opioid agonists and have been discussed previously in this chapter. In particular, the increased incidence of vomiting after morphine administration, as well as its potential to cause histamine release after intravenous administration, distinguish morphine from other full opioid agonists.

Oxymorphone Oxymorphone is a synthetic opioid that acts as a full agonist at μ receptors and is comparable with morphine in its analgesic efficacy and duration of action. It is a more lipid-soluble drug than morphine and is readily absorbed after intramuscular or subcutaneous administration. Oxymorphone is not available as an oral formulation.

When compared with morphine, oxymorphone may be less likely to cause vomiting and tends to produce more sedation when administered to domestic species. Its respiratory depressant effects are similar to those induced by morphine, but oxymorphone seems more likely to cause panting in dogs. It does not produce histamine release, even when administered intravenously (Smith et al. 2001). Oxymorphone's other side effects are typical of other full μ agonist opioids and have been discussed previously.

Hydromorphone Hydromorphone is a synthetic opioid that acts as a full agonist at μ receptors and is used in both human and veterinary medicine. Clinically, hydromorphone and oxymorphone have similar efficacy, potency, duration of analgesic action, and side effect profiles, but hydromorphone remains significantly less expensive. Like oxymorphone, hydromorphone is not associated with histamine release so bolus intravenous administration is considered safe (Smith et al. 2001).

Meperidine Meperidine is a synthetic opioid that exerts its analgesic effects through agonism at μ receptors. Interestingly, it also appears able to bind other types of receptors, which may contribute to some of its clinical effects other than analgesia. Meperidine is capable of blocking sodium channels and inhibiting activity in dorsal horn neurons in a manner analogous to local anesthetics (Wagner et al. 1999; Wolff et al. 2004). It has also recently been shown that meperidine exerts agonist activity at alpha-2 receptors, specifically the $alpha_{2B}$ subtype, suggesting that it may possess some alpha-2 agonist-like properties (Takada et al. 1999, 2002).

Meperidine has a considerably shorter duration of analgesic action compared to morphine, oxymorphone, or hydromorphone, typically not extending beyond 1 hour (Branson et al. 2001). Metabolic pathways vary among different species but, in general, most of the drug is demethylated to normeperidine in the liver and then undergoes further hydrolysis and ultimately renal excretion (Branson et al. 2001; Taylor et al. 2001; Yeh et al. 1981). Normeperidine is an active metabolite and possesses approximately one-half the analgesic efficacy of meperidine (Branson et al. 2001; Gutstein & Akil 2001). Normeperidine has produced toxic neurologic side effects in human patients receiving meperidine for prolonged periods of time, especially in the presence of impaired renal function (Stoelting 1999; Stone et al. 1993).

Unlike most of the other opioids in clinical use, meperidine has been shown to produce significant negative inotropic effects when administered alone to conscious dogs (Priano & Vatner 1981). Also, due to its modest atropine-like effects, meperidine tends to increase heart rate rather than predispose to bradycardia, as is often seen with other opioids (Branson et al. 2001; Stoelting 1999). The clinical significance of these cardiovascular effects in the perianesthetic period has never been clearly ascertained. Like morphine, meperidine also causes histamine release when administered intravenously (Branson et al. 2001).

A rare but life-threatening drug interaction has been reported in human patients receiving meperidine that may have relevance in veterinary medicine. The combination of meperidine (and perhaps other opioids) with a monoamine oxidase inhibitor may lead to "serotonin syndrome," which is characterized by a constellation of symptoms, including confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, and diarrhea (Bowdle 1998; Heinonen & Myllyla 1998; Sporer 1995; Tissot 2003). A monoamine oxidase inhibitor, selegiline (Deprenyl®), has been used in dogs to treat pituitary-dependent hyperadrenocorticism or to modify behavior in patients with canine cognitive dysfunction. Though there have not, to date, been any reports of adverse meperidine-selegiline interactions in dogs, the veterinarian must be aware of the potential for complications if analgesia is required in patients receiving monoamine oxidase inhibitors. A recent study has evaluated the effects of other opioids (oxy-

morphone and butorphanol) in selegiline-treated dogs and did not identify any specific adverse drug interactions in these animals (Dodam et al. 2004).

Fentanyl Fentanyl is a highly lipid soluble, short-acting synthetic μ opioid agonist. A single dose of fentanyl administered intravenously has a more rapid onset and a shorter duration of action than morphine. Peak analgesic effects occur in about 5 minutes and last approximately 30 minutes (Gutstein & Akil 2001; Stoelting 1999). Rapid redistribution of the drug to inactive tissue sites, such as fat and skeletal muscle, leads to a decrease in plasma concentration and is responsible for the prompt termination of clinical effects. In most veterinary species the elimination half-time after a single bolus or a brief infusion is in the range of 2–3 hours (Carroll et al. 1999; Lee et al. 2000; Maxwell et al. 2003). Administration of very large doses or prolonged infusions may result in saturation of inactive tissues with termination of clinical effects becoming dependent on hepatic metabolism and renal excretion (Gutstein & Akil 2001; Stoelting 1999). Thus, the context-sensitive half-time of fentanyl increases significantly with the duration of the infusion, and clinical effects may persist for an extended period following termination of a long-term intravenous infusion.

Side effects associated with fentanyl administration are similar to those of the other full μ agonist opioids. In general, cardiovascular stability is excellent with fentanyl, and intravenous administration is not associated with histamine release (Gutstein & Akil 2001; Stoelting 1999). Bradycardia may be significant with bolus doses but readily responds to anticholinergics if treatment is warranted (Branson et al. 2001; Gutstein & Akil 2001). In human patients, muscle rigidity, especially of the chest wall, has been noted after administration of fentanyl or one of its congeners (Bowdle 1998; Fahnenstich et al. 2000; Muller & Vogtman 2000). The potential significance of this adverse effect in animal patients is not clear at this time, and the risk is considered minimal if large rapid bolus administrations are avoided.

Clinically, fentanyl is used most frequently in dogs and cats, but it is also a potentially useful analgesic in other species, including the horse, cow, sheep, goat, and pig. Historically, fentanyl was available in combination with the butyrophenone tranquilizer, droperidol, in a product called Innovar-Vet, which was typically administered in the preanesthetic period to provide sedation and analgesia. This product is no longer available, and systemic administration of fentanyl today is usually via the intravenous route.

The development of novel less invasive routes of opioid administration for use in human patients led to the marketing of transdermal fentanyl patches (Duragesic®). The patches are designed to release a constant amount of fentanyl per hour, which is then absorbed across the skin and taken up systemically. Fentanyl patches are designed for human skin and body temperature, however, their use has been evaluated in a number of domestic veterinary species (Carroll et al. 1999; Egger et al. 1998, 2003; Franks et al. 2000; Gellasch et al. 2002; Gilberto et al. 2003; Maxwell et al. 2003; Robinson et al. 1999; Wilkinson et al. 2001). Substantial variations in plasma drug concentrations have been documented, and significant lag times after patch placement are common prior to onset of analgesia (Carroll et al. 1999; Egger et al. 1998, 2003; Lee et al. 2000). Furthermore, changes in body temperature have been shown to significantly affect fentanyl absorption in anesthetized cats, and it is likely that other factors associated with skin preparation and patch placement have the potential to substantially alter plasma fentanyl levels and analgesic efficacy (Pettifer & Hosgood 2003). Fentanyl patch safety and efficacy in most species is unknown at this time.

Alfentanil, Sufentanil, and Remifentanil Alfentanil, sufentanil, and remifentanil are all structural analogues of fentanyl that were developed for use in humans in an effort to create analgesics with a more rapid onset of action and predictable termination of opioid effects. All three are similar with regard to onset, and all have context-sensitive half-times that are shorter than that of fentanyl after prolonged infusions (Stoelting 1999) Remifentanil is unique among opioids because it is metabolized by nonspecific plasma esterases to inactive metabolites (Chism & Rickert 1996; Hoke et al. 1997). Thus, hepatic or renal dysfunction will have little impact on drug clearance and this, in combination with the robust nature of the esterase metabolic system, contributes to the predictability associated with infusion of remifentanil (Gutstein & Akil 2001; Stoelting 1999).

All three of these drugs are used during general anesthesia for procedures requiring intense analgesia and/or blunting of the sympathetic nervous system response to noxious stimulation. As yet, they have limited applications for postoperative or chronic pain management. Like fentanyl, they can be administered at relatively low infusion rates as adjuncts to general anesthetic protocols based on volatile inhalant or other injectable agents, or they can be administered at higher rates as the primary agent for total intravenous anesthesia. The minimum alveolar anesthetic concentration-sparing properties of these agents have been demonstrated in both the dog and cat (Hoke et al. 1997; Ilkiw et al. 1997; Mendes & Selmi 2003; Michelsen et al. 1996; Pascoe et al. 1997). In the horse, systemic infusions of alfentanil did not have significant effects on minimum alveolar concentrations of inhalant anesthetics and when administered to conscious horses were associated with increases in locomotor activity (Pascoe & Taylor 2003; Pascoe et al. 1991, 1993). There is little evidence to suggest that any of the

fentanyl analogues offer advantages over morphine when administered into the epidural space for analgesia (Natalini & Robinson 2000).

Methadone Methadone is a synthetic μ opioid agonist with pharmacologic properties qualitatively similar to those of morphine, but possessing additional affinity for N-methyl-D-aspartate receptors (Gorman et al. 1997; Ripamonti & Dickerson 2001). Methadone's unique clinical characteristics include excellent absorption following oral administration, no known active metabolites, high potency, and an extended duration of action (Branson et al. 2001; Gutstein & Akil 2001; Ripamonti & Dickerson 2001). In human patients, the drug has been used primarily in the treatment of opioid abstinence syndromes, but is being used increasingly for the management of chronic pain. Though there are reports of intramuscular or intravenous administration of methadone in the perioperative period in dogs, cats, and horses, the drug is not commonly used in this setting in North America at this time (Dobromylskyj 1996; Fisher 1984; Kramer et al. 1996).

Codeine Codeine is the result of substitution of a methyl group onto morphine, which acts to limit first-pass hepatic metabolism and accounts for codeine's high oral bioavailability (Gutstein & Akil 2001; Stoelting 1999). Codeine is well known for its excellent antitussive properties and is often combined in an oral formulation with a non-opioid analgesic, such as acetaminophen (Tylenol 3®), for the management of mild to moderate pain in human patients.

Oxycodone and Hydrocodone Oxycodone and hydrocodone are opioids that are typically administered orally for the treatment of pain in human patients. Though oxycodone is available as a single-drug continuous-release formulation (Oxycontin®), these drugs are most often prepared in combination with nonopioid analgesics, such as aspirin and acetaminophen (Percocet®, Percodan®, Lorcet®, Vicodan®, etc.). Little has been published regarding the use of these opioids in veterinary species.

Etorphine and Carfentanil (M-99® and Wildnil®, Respectively) These two opioids are discussed together because they are both used exclusively for the restraint and capture of wild animals, rather than as analgesic agents. They are extremely potent opioids, and the immediate availability of a suitable antagonist is mandatory before these drugs are to be used, not only to reverse drug effects in animal patients, but also as a safety precaution in the event of accidental human injection. Though etorphine and carfentanil are most often injected intramuscularly (usually using a remote drug delivery technique), recent studies suggest that carfentanil is useful when administered orally in a variety of species, including the brown bear, the Brazilian tapir, and the chimpanzee (Kearns et al. 2000; Mama et al. 2000; Mortenson & Bechert 2001; Pollock & Ramsay 2003). A number of different drugs have been used in combination with etorphine or carfentanil to enhance muscle relaxation, including acepromazine, xylazine, and medetomidine (Caulkett et al. 2000; Miller et al. 2003; Ramdohr et al. 2001; Roffe et al. 2001).

Thiafentanil Thiafentanil is an opioid agonist that has been utilized to facilitate capture of several species of birds and mammals (Borkowski et al. 2009; Cushing & McClean 2010; Grobler et al. 2001; Kilgallon et al. 2010). It is pharmacologically classified as a synthetic opioid that has a relatively short duration of action. The shorter duration of action in combination with its reversibility with the opioid antagonist naltrexone make it an attractive agent when long periods of narcotization are not desirable.

Opioid Agonist–Antagonists and Partial Agonists

This group includes drugs that have varying opioid receptor binding profiles, but which have one thing in common: they all occupy μ opioid receptors, but do not initiate a maximal clinical response. Drugs such as butorphanol and nalbuphine are classified as agonist–antagonists. They are competitive μ receptor antagonists, but exert their analgesic actions by acting as agonists at κ receptors (Fig. 1.2). Buprenorphine, on the other hand, is classified as a partial agonist and binds

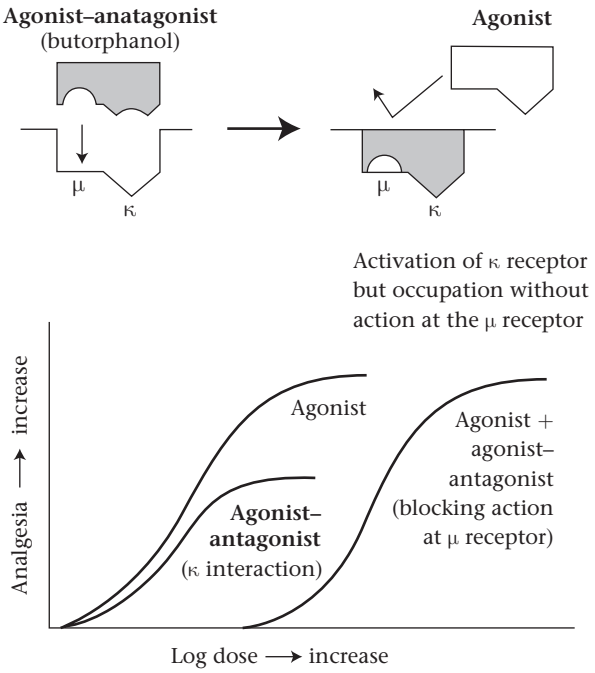

Figure 1.2. Activation of κ receptor, but occupation without action at the μ receptor.

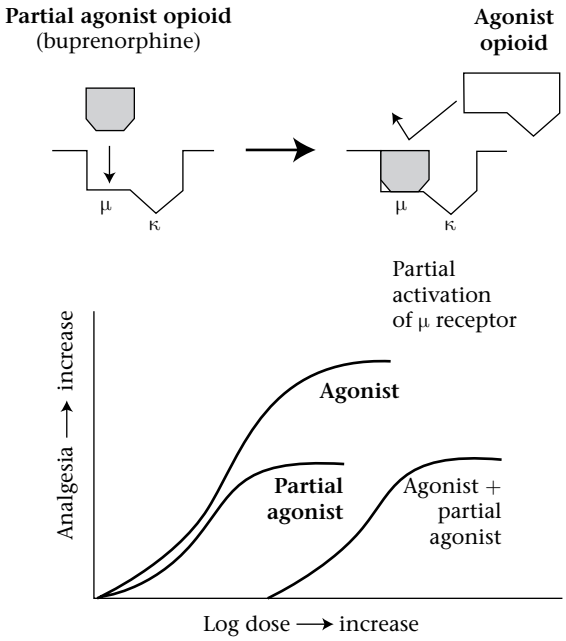

Figure 1.3. Partial activation of μ receptor.

μ receptors but produces only a limited clinical effect (Fig. 1.3). These mixed agonist–antagonist drugs were developed for the human market in an attempt to create analgesics with less respiratory depression and addictive potential. Due to their opioid receptor-binding affinities, the side effects associated with these drugs demonstrate a so-called ceiling effect, whereby increasing doses do not produce additional adverse responses. Unfortunately, the benefits of this ceiling effect on ventilatory depression come at the expense of limited analgesic efficacy and only a modest ability to decrease anesthetic requirements.

The coadministration of opioids with differing receptor binding profiles is currently an active area of research that deserves further attention. The interactions in this setting are complex and it appears that opioid coadministration has the potential to produce additive, synergistic, or antagonistic analgesic effects depending on the particular species, dosage, drugs, and pain model being evaluated. The following section contains brief descriptions of opioid agonist–antagonists and partial agonists that are currently used in veterinary medicine.

Butorphanol Butorphanol is a synthetic agonist–antagonist opioid and has been used extensively in a wide variety of veterinary species. The drug was originally labeled as an antitussive agent in dogs and, even now, is approved as an analgesic in the cat and horse only (Branson et al. 2001). Butorphanol exerts its relevant clinical effects through its interactions at κ receptors and acts as an antagonist at μ receptors. The duration of butorphanol's analgesic effects remains somewhat debatable and likely varies with species, type and intensity of pain, dosage, and route of administration (Sawyer et al. 1991; Robertson et al. 2003a; Sellon et al. 2001). In general, its effects are shorter lived than those of morphine and are probably in the range of 1–3 hours. Butorphanol does not induce histamine release when administered intravenously and has minimal effects on cardiopulmonary function. There is conflicting evidence regarding the effects of butorphanol on inhalant anesthetic requirements in the dog, cat, and horse. Earlier studies failed to demonstrate a significant sparing effect on minimum alveolar concentration when butorphanol was co-administered with halothane in dogs and ponies (Doherty et al. 1997; Matthews & Lindsay 1990; Quandt et al. 1994). More recently, isoflurane MAC reductions have been documented after administration of clinically relevant doses of butorphanol in both dogs and cats (Ilkiw et al. 2002; Ko et al. 2000). Reasons for these discrepancies are probably related to differences in study techniques and, in the dog and cat specifically, it seems that butorphanol is capable of inducing at least modest reductions in inhalant anesthetic requirements.

Traditionally, it was thought that the simultaneous or sequential administration of butorphanol with a pure μ opioid agonist, such as morphine or hydromorphone, would be counterproductive from an analgesic standpoint because butorphanol's ability to antagonize μ receptors could inhibit or even reverse the effects of the agonist drug. Certainly, it has been clearly demonstrated that excessive sedation associated with a pure μ agonist can be partially reversed by the administration of low doses of butorphanol, and it was presumed that butorphanol would similarly reverse the μ-mediated analgesic effects as well. It would now appear that the potential interactions between butorphanol and full μ opioid agonists are more complex than originally believed. One study demonstrated that coadministration of butorphanol and oxymorphone to cats subjected to a visceral noxious stimulus resulted in enhanced analgesic effects (Briggs et al. 1998). A more recent feline study, however, evaluated the combination of butorphanol and hydromorphone in a thermal threshold pain model and failed to demonstrate enhanced analgesia and suggested that butorphanol did, in fact, inhibit hydromorphone's analgesic effects (Lascelles & Robertson 2004). These contradictory findings illustrate that we still have much to learn about coadministration of opioid agents with differing receptor-binding profiles and the clinical effects produced by such co-administration likely depend on many factors, including species, type of pain, dose, and the specific drugs involved.

Nalbuphine and Pentazocine Nalbuphine and pentazocine are classified as agonist–antagonist opioids and are clinically similar to butorphanol. They induce mild

analgesia accompanied by minimal sedation, respiratory depression, or adverse cardiovascular effects. Like butorphanol, nalbuphine is occasionally used to partially reverse the effects of a full μ agonist opioid while maintaining some residual analgesia.

Buprenorphine Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine. Unlike other opioids in this category, buprenorphine is considered to be a partial agonist at μ opioid receptors. The drug binds avidly to and dissociates slowly from μ receptors, but is not capable of eliciting a maximal clinical response. Due to its receptor-binding characteristics, buprenorphine has a delayed onset of action and takes at least 60 minutes to attain peak effect after intramuscular administration. It also has a relatively long duration of action with clinical analgesic effects persisting for 6–12 hours in most species. Also, its high affinity for the μ receptor means that it may be difficult to antagonize its effects with a drug, such as naloxone. Buprenorphine has most often been administered intravenously or intramuscularly; however, due to the long lag time before clinical effects are achieved after intramuscular administration, the intravenous route is preferred. Comparable plasma drug levels and analgesic efficacy with oral transmucosal administration versus intravenous administration has been demonstrated in cats (Robertson et al. 2003b). Compounded versions of buprenorphine are widely available and include higher concentrations for convenient dosing to larger animals and sustained release formulations for increased duration of action. If sustained release preparations are used, there should be a plan for supportive care should significant adverse effects occur since complete reversal of buprenorphine with conventional antagonists is often unsuccessful.

Opioid Antagonists

These drugs have high affinities for the opioid receptors and are able to displace opioid agonists from μ and κ receptors. After this displacement, the pure antagonists bind to and occupy opioid receptors, but do not activate them (Fig. 1.4). Under ordinary circumstances, in patients that have not received exogenous agonist opioids, the opioid antagonists have few clinical effects when administered at clinically relevant dosages (Gutstein & Akil 2001). It is important to recognize that these drugs will rapidly reverse all opioid-induced clinical effects including analgesia.

Naloxone This pure opioid antagonist is capable of reversing all opioid agonist effects, producing increased alertness, responsiveness, coordination and, potentially, increased perception of pain. Naloxone's duration of action is shorter than many of the opioid agonists, with recommended intravenous doses lasting between 30 and 60 minutes. Consequently, animals need to be closely monitored for renarcotization after a dose of naloxone. Occasionally, excitement or anxiety may be seen after naloxone reversal of an opioid agonist. Premature ventricular contractions have also been documented after reversal, but are not a common occurrence and seem to be more likely if there are high levels of circulating catecholamines. This drug is sometimes administered sublingually to neonatal patients exhibiting respiratory depression that have been delivered by cesarean section after maternal administration of an opioid agonist.

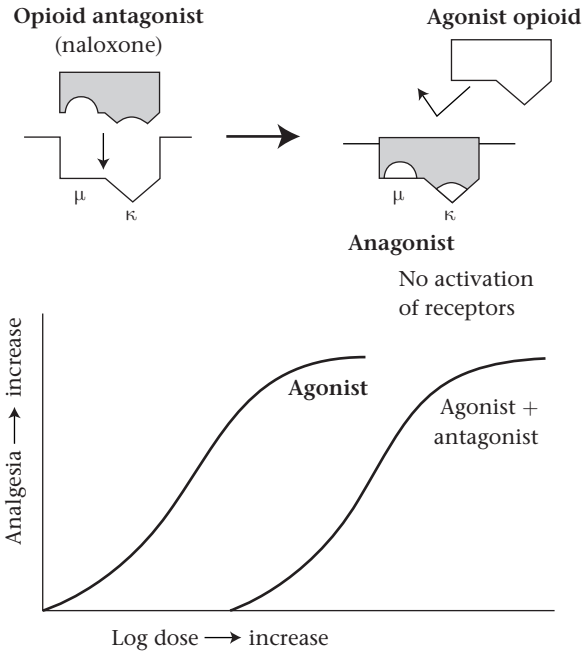

Figure 1.4. No activation of receptors.

Nalmefene and Naltrexone Both of these drugs are pure opioid antagonists with clinical effects that last approximately twice as long as naloxone (Veng-Pedersen et al. 1995). Though little is published about the use of these drugs in veterinary patients, they may be advantageous in preventing renarcotization when used to antagonize the effects of a long-acting opioid.

NONSTEROIDAL ANTI-INFLAMMATORIES

The nonsteroidal antiinflammatory drugs (NSAIDs) relieve mild to moderately severe pain and have been used extensively in a wide variety of domestic animals for many years. While pharmacokinetic and pharmacodynamic studies involving NSAIDs in wild and exotic animals are lacking, their use in such species continues to increase.

This class of drugs dates back thousands of years with the salicylates being among the oldest and still

most commonly used analgesics (Vane & Botting 2003). Salicylate is a naturally occurring substance found in willow bark and was used for centuries to manage pain associated with rheumatism prior to production of the synthetic compound. In 1878, Felix Hoffman working at the Bayer company in Germany made the acetylated form of salicylic acid which has come to be known as aspirin (Vane & Botting 2003). While aspirin (acetylsalicylic acid or ASA) has been found to be effective in the management of acute and chronic mild discomfort, the newer injectable NSAIDs appear to have comparable efficacy to the pure μ agonist opioids in controlling moderate to severe soft tissue and orthopedic pain. The NSAIDs appear to confer synergism when used in combination with opioids and may demonstrate an opioid sparing effect should lower dosages of opioid be required. Their extended duration of action, in addition to their analgesic efficacy make the NSAIDs ideal for treating acute and chronic pain in veterinary species. Careful patient and drug selection is critical, however, due to their potential for harmful side effects.

The Cyclooxygenases and Prostaglandin Synthesis

In 1971, Vane discovered the mechanism by which aspirin exerts its antiinflammatory, analgesic and antipyretic actions. He proved that aspirin and other NSAIDs inhibited the activity of a cyclooxygenase (COX) enzyme, which produced prostaglandins (PGs) involved in the pathogenesis of inflammation, swelling, pain, and fever (Vane 1971). Twenty years later, the discovery of a second COX enzyme was made, and more recently, a newly identified COX-3 (Botting 2000, 2003; Chandrasekharan et al. 2002). Cyclooxygenase (previously termed prostaglandin synthase) oxidizes arachidonic acid (previously termed eicosatetraenoic acid) to various eicosanoids (including PGs and other related compounds) (Fig. 1.5) (Livingston 2000). Oxidation of arachidonic acid by 5-lipoxygenase (5-LOX), the most biologically important of the mammalian oxygenases, results in the series of eicosanoids termed leukotrienes (Fig. 1.5). The release of arachidonic acid from membrane phospholipid is catalyzed by the

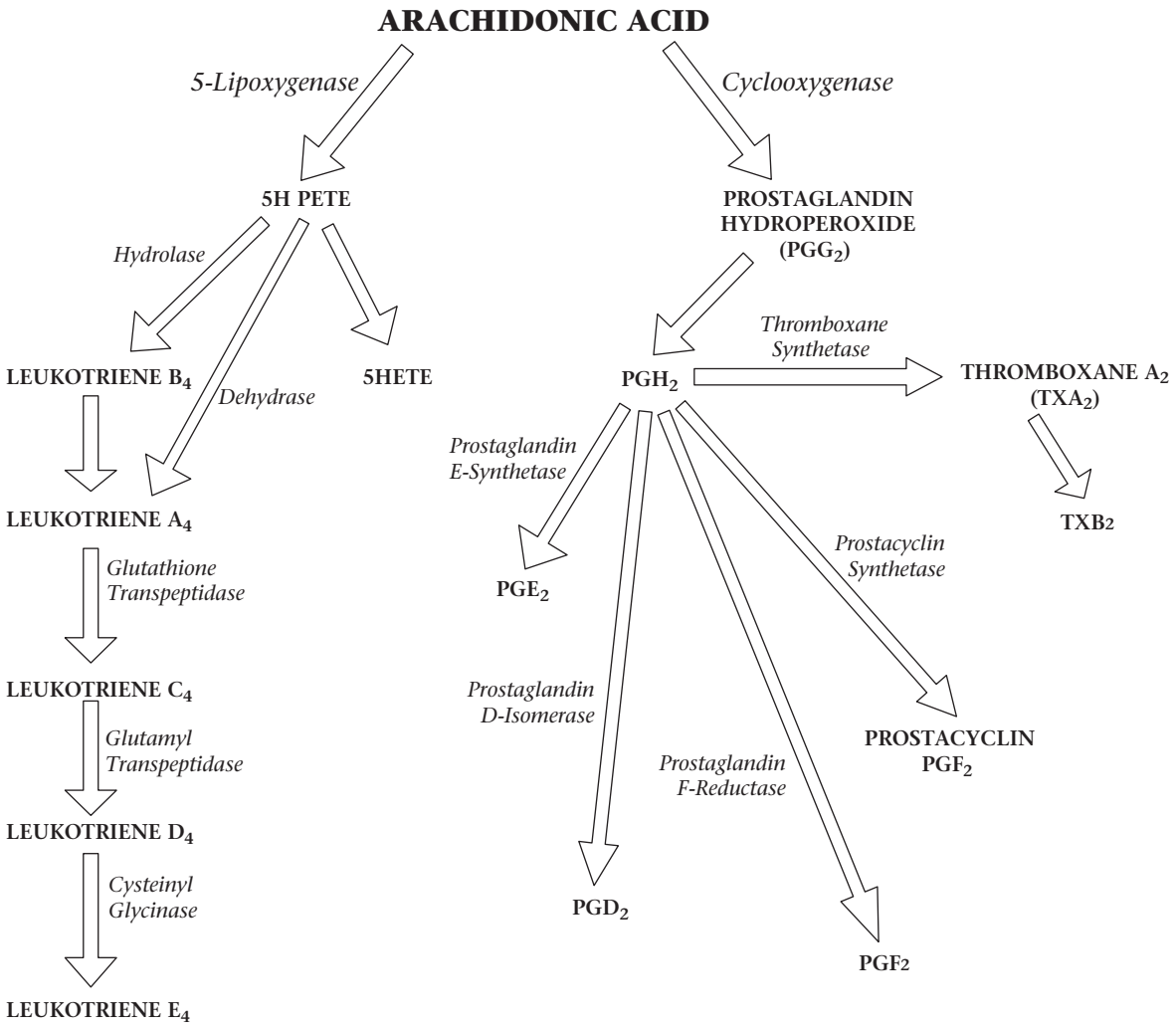

Figure 1.5. Eicosanoid synthesis.

enzyme phospholipase A_2 and is the rate-limiting step in PG and leukotriene synthesis. Prostaglandin G_2 is the initial prostenoid formed, followed by prostaglandin H_2, which serves as a substrate for prostaglandin E-synthetase, prostaglandin D-isomerase, prostaglandin F-reductase, prostacyclin synthetase, and thromboxane synthetase for conversion to a variety of other prostenoids ubiquitous throughout cells and tissues in the body (Livingston 2000). These include the PGs PGE_2, PGD_2, PGF_2, and PGI_2 (prostacyclin), and the thromboxanes TXA_2 and TXB_2, all with diverse functions (Vane & Botting 1995). The PGs are not stored but are synthesized at a constant rate. They have short half-lives of 4–6 minutes at 37°C, and act locally at the site of production.

The PGs produced by both COX-1 and COX-2 are ubiquitous throughout the body and serve to facilitate many normal physiologic functions during both health and illness. Consequently, the clinical use of NSAIDs has the potential to disrupt these functions with the possibility of significant organ dysfunction. Thus, in addition to their role as analgesics, the effects of NSAIDs on the constitutive functions of the PGs must always be considered. There are several key points to note: (1) COX-1 generates PGs that are responsible for "mucosal defense" (i.e., secretion of bicarbonate and mucus, mucosal blood vessel attenuation of constriction, and mucosal epithelial regeneration), as well as thromboxane A_2, which is necessary for platelet function; (2) COX-2 produces PGs, which function in the prevention and promotion of healing of mucosal erosions, exert antiinflammatory effects by inhibiting leukocyte adherence, as well as play a role in renal protection and maturation; and (3) COX-3 produces PGs, which exert a protective function by initiating fever (Botting 2003; Vane & Botting 1995).

Thus, depending on the NSAID selected, primary plug formation of platelets, modulation of vascular tone in the kidney and gastric mucosa, cytoprotective functions within the gastric mucosa, smooth muscle contraction, and regulation of body temperature will all be affected (Vane & Botting 1995). However, in this regard, not all NSAIDs are created equal. As noted above, the COX-1, COX-2, and COX-3 enzymes make variable contributions to these functions, and individual NSAIDs inhibit each of these enzymes differently. Some NSAIDs inhibit both COX-1 and COX-2, (i.e., aspirin, phenylbutazone, ketoprofen/Anafen®, ketorolac/Toradol®, and flunixin meglumine/Banamine®); other NSAIDs preferentially inhibit COX-2 with only weak inhibition of COX-1 (i.e.. meloxicam/Metacam®, carprofen/Rimadyl®, etodolac/Etogesic®, vedaprofen/Quadrisol-5®, and tolfenamic acid/Tolfedine®); others inhibit COX-2 exclusively (i.e.. deracoxib/Deramax®, firacoxib/Prevacox®, Robenacoxib/Onsior®, and mavicoxib/Trocoxcil®); while still another drug, acetaminophen, only weakly inhibits both COX-1 and COX-2, but is able to inhibit COX-3 activity preferentially (Botting 2000).

Several *in vitro* studies investigating NSAID selective inhibition of the COX-1 and COX-2 isoenzymes have been published; however, these are very difficult to interpret due to inconsistencies in the assays used (Kay-Mugford et al. 2000). Clinically, this information is confusing as it does not consider the PK of particular drugs and their concentrations in various tissues (Bertolini et al. 2001). Most NSAIDs that inhibit COX have been shown to result in diversion of arachidonate to the 5-LOX pathway. The 5-LOX is principally found in polymorphonuclear cells, mast cells, monocytes, basophils, and B lymphocytes that are recruited during inflammatory and immune reactions (Bertolini et al. 2001). This enzyme catalyzes the initial step in leukotriene biosynthesis, which subsequently produces various eicosanoids, with LTB_4 being the most notable potent mediator of inflammation. The excessive production of leukotrienes has been implicated in the creation of NSAID-induced ulcers (Hudson et al. 1993; Rainsford 1992). As always, however, the biological system is not clear-cut. While the LOX pathway is proinflammatory, there is also an anti-inflammatory pathway, which is discussed in more detail later (Serhan & Chiang 2004).

The contribution of the leukotrienes to the inflammatory process would seem to suggest that inhibition of both the COX and 5-LOX pathways by a therapeutic agent would result in an enhanced safety profile and may confer even greater analgesic efficacy due to broader anti-inflammatory and anti-nociceptive effects (Kirchner et al. 1997b). Data available show that dual-acting compounds are effective in arthritic models, where they also retain anti-thrombotic activity, produce little or no gastrointestinal damage, and do not adversely affect the asthmatic state (Bertolini et al. 2001). A recently approved dual COX/5-LOX inhibitor (tepoxalin/Zubrin®) has undergone clinical trials and is now approved for veterinary use (Kirchner et al. 1997b; Argentieri et al. 1994). Tepoxalin has demonstrated gastrointestinal antiinflammatory activity in mice, supporting the theory that 5-LOX inhibition has the potential to play a vital role in the prevention of NSAID-induced gastric inflammation (Kirchner et al. 1997a).

The NSAIDs and Mechanisms of Analgesia

Prostaglandins, notably PGE_2 and prostacyclin, are potent mediators of inflammation and pain. These molecules exert hyperalgesic effects and enhance nociception produced by other mediators, such as bradykinin. The NSAIDs' analgesic mechanism of action is through inhibition of COX-1, COX-2, and COX-3, activity with subsequent prevention of PG synthesis.

The antinociceptive effects of the NSAIDs are exerted both peripherally and centrally (Chopra et al. 2000).

The NSAIDs penetrate inflamed tissues where they have a local effect, which makes them excellent analgesic choices for injuries with associated inflammation, as well as conditions such as synovitis, arthritis, cystitis, and dermatitis (Chopra et al. 2000). The central action is at both the spinal and supraspinal levels, with contributions from both COX-1 and COX-2 (Chopra et al. 2000; McCormack 1994; Malmberg & Yaksh 1992; Yaksh et al. 1998). This central effect may account for the overall well-being and improved appetite that is often observed in patients receiving parenterally administered NSAIDs for relief of acute pain.

The rational use of NSAIDs as analgesics should be based on an understanding of pain physiology and pathophysiology. Nociceptive pathways may involve either the COX-1 or COX-2 gene, and these genes are expressed in different locations and under different circumstances. The COX-2 isoenzyme is known as the inducible isoform because it is upregulated in inflammatory states and is known to play a key role in nociception. While the COX-1 gene has traditionally been thought of as being expressed constitutively, this isoenzyme also plays an integral role in the pain experience (Chandrasekharan et al. 2002). The COX-1 selective NSAIDs are superior to COX-2 selective NSAIDs at inhibiting visceronociception caused by chemical pain stimulators in a mouse peritoneal model (Ochi et al. 2000). This has been confirmed by visceronociception being greatly reduced in COX-1 but not COX-2 knockout mice (Ballou et al. 2000). These studies concluded that peripheral COX-1 mediates nociception in slowly developing pain in mice, such as in visceral pain, and central COX-1 may be involved in rapidly transmitted, nonvisceral pain, such as that caused by thermal stimulation (Ballou et al. 2000). Visceral pain may be mediated, at least in part, by stimulation of intraperitoneal receptors located on sensory fibers by COX-1-produced prostacyclin (Botting 2003). Interestingly, there may be gender differences, as in Ballou's mouse model, which demonstrated that spinal COX-2 did in fact contribute to visceral nociception, but only in female mice (Ballou et al. 2000). The analgesic potency of a range of NSAIDs in relieving tooth extraction pain in humans correlates closely with increasing selectivity toward COX-1 rather than COX-2. These findings highlight the importance of both COX-1 and COX-2 contributions to pain and the selective efficacy of the NSAIDs in treating various painful conditions.

The COX-2 or inducible isoenzyme can potentially increase by 20-fold over baseline in the presence of tissue injury and inflammation (Malmberg & Yaksh 1992). Pro-inflammatory cytokines and mitogens, such as interleukin-1-beta, (IL-β), interferon gamma, and tumor necrosis factor-alpha (TNF-α), induce COX-2 expression in macrophages, as can platelet-activating factor (PAF), and PGE_2 (Bertolini et al. 2001). These events may also occur in chondrocytes, osteoblasts and synovial microvessel endothelial cells. The higher COX levels increase prostenoid production, where these compounds serve as amplifiers of nociceptive input and transmission in both the peripheral and central nervous systems (Malmberg & Yaksh 1992). The COX-2 selective NSAIDs have been shown to be clinically useful in managing inflammatory pain in humans and animals. This has been a focus of the pharmaceutical industry, as a selective COX-2 inhibitor may potentially show efficacy in alleviating pain and hyperalgesia while sparing COX-1 constitutive activity and potential adverse effects associated with NSAID administration. Unfortunately, the biological system is not as simple as first envisioned. While COX-2 is induced during inflammation, it has also been shown to be induced during resolution of the inflammatory response where the antiinflammatory PGs (PGD_2 and $PGF_{2\alpha}$), but not pro-inflammatory PGE_2, are produced. Potentially, inhibition of COX-2 during this phase may actually prolong inflammation (Bertolini et al. 2001). As is the case for COX-1, it now appears that the COX-2 isoenzyme also has important constitutive functions. Studies indicate there may be a protective role for COX-2 in maintenance of gastrointestinal integrity, ulcer healing, and in experimental colitis in rats (DuBois et al. 1998; Reuter et al. 1996; Schmassmann et al. 1998). In addition, the COX-2 isoenzyme appears to have constitutive functions associated with nerve, brain, ovarian and uterine function, and bone metabolism (DuBois et al. 1998). Therefore, the potential for NSAID associated side effects with these systems is of concern. Of major importance are the COX-2 constitutive functions within the kidney which differ from those of COX-1 in hypotensive and hypovolemic states (Imig 2000). Also, COX-2 appears to be important in nephron maturation (Harris 2000). The canine kidney is not fully mature until three weeks after birth, and administration of a NSAID during this time, or to the bitch prior to birth, may cause a permanent nephropathy (Horster et al. 1971). In fact, in COX-2 null mice which lack the gene for COX-2, all animals die before 8 weeks of age from renal failure (Morham et al. 1995). This does not occur in COX-1 null mice, and interestingly, these mice did not develop gastric pathology (Morham et al. 1995).

When considering the COX selectivity of a particular NSAID, the concentration (i.e., dose) of the NSAID may also influence its actions. A drug may function as a competitive, nonpreferential ,or selective COX inhibitor (COX-1 or COX-2) at higher concentrations, and as a COX-2 selective inhibitor at lower concentrations (Lipsky et al. 2000). The significance of this is the potential for inhibition of COX-1 with administration of an allegedly COX-2 selective NSAID. The COX selectivity may be present *in vitro*, however, at the dosing required to achieve analgesia, such selectivity may be lost. Cloning studies comparing canine COX isoenzymes with human COX isoenzymes found that they

are highly homologous (Gierse et al. 2002). Canine COX-1 and COX-2 had a 96% and 93% DNA sequence homology, respectively, with their human counterparts. This suggests that they would be similarly affected by pharmaceuticals, such as NSAIDs designed to inhibit their function. However, the distribution of the COX enzymes may differ among species. When summarizing the common adverse effects noted in veterinary patients following administration of NSAIDs (ie. gastrointestinal ulceration, renal perturbations, and hemorrhage), hemorrhage is the only one that appears to be spared with COX-2 selective NSAIDs in animals with normal platelet numbers and function.

Cyclooxygenase-2 is reduced following administration of glucocorticoids, which may partially explain the antiinflammatory and analgesic effects of this class of medications. Of interest, in addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of a number of epithelial cell-origin carcinomas, including colon, esophagus, breast, and skin, and in Alzheimer's disease and other neurological conditions (Fosslien 2000; Lipsky 1999; Smalley & DuBois 1997). The COX-2 inhibitors are being researched as potential anti-carcinogenic agents (FitzGerald & Patrono 2001).

Dissecting out the details of the derivation and specific actions of COX-1 and COX-2 continues to provide important insight into the management of pain with NSAIDs. The picture, however, remains incomplete, as some NSAIDS do not significantly inhibit these enzymes. This finding stimulated the search for a potential COX-3 isoenzyme. Based on studies using canine cortex, a COX-3 isoenzyme was discovered that was derived from the same gene as COX-1 (Chandrasekharan et al. 2002). The COX-3 isoenzyme is also present in human brain and heart tissues. It is distinct from COX-1 and -2, as demonstrated in studies using common analgesic/antipyretic NSAIDS in suppressing COX production. Acetaminophen inhibited COX-3 activity, but not COX-1 and -2, as did dipyrone (Chandrasekharan et al. 2002). Both of these agents are frequently used to reduce fever in animals. Other analgesic/antipyretic NSAIDs found to be effective COX-3 inhibitors are diclofenac (the most potent), and aspirin and ibuprofen (which preferentially inhibit COX-3 over COX-1 and -2). The overall conclusion of this particular study was that COX-3 possesses COX activity that differs pharmacologically from both COX-1 and -2, but is more similar to COX-1 (Chandrasekharan et al. 2002). This study also reported that the COX-3 isoenzyme is more susceptible to inhibition by drugs that are analgesic and antipyretic but which lack anti-inflammatory activity. This observation again emphasizes the potential utility of administering NSAIDs with different COX selectivities for managing pain of different etiologies. As the COX-3 isoenzyme genetic profile is derived from the COX-1 gene, it appears that the COX-1 gene plays an integral role in pain and/or fever, depending on the physiologic context (Chandrasekharan et al. 2002). This has been confirmed by the studies mentioned earlier (Ballou et al. 2000; Botting 2003; Ochi et al. 2000). The COX-1 selective NSAIDs used in veterinary and human patients with poor central nervous system penetration (i.e., ketoprofen and ketorolac) may, in fact, reach sufficient concentrations in the brain to inhibit COX-3 (Warner et al. 1999). It is also recognized that the analgesic effects of these NSAIDs frequently occur at lower dosages than those required to inhibit inflammation.

The NSAIDs and Fever

Just as the relationship between pain and the various activities of the COX system is complex, so too is the association between fever and the COX isoenzymes. The mechanisms leading to the generation of fever vary depending on the inciting factor that may be peripheral (i.e., endotoxin) or central (i.e., endogenous pyrogens, such as IL-1). Interspecies variation is also substantial, and the definitive role of the COXs in pyresis remains to be clearly elucidated. Evidence suggests that COX-2 plays a role in endotoxin pyrexia while, based on the antipyretic effects of acetaminophen and aspirin, COX-1 and COX-3 appear to function in endogenous pyrexia (Botting 2000, 2003; Chandrasekharan et al. 2002).

The NSAIDs and Endogenous Antiinflammatory Mechanisms

Endogenously generated small chemical mediators, or autacoids, play a key role in controlling inflammation by inhibiting polymorphonuclear cell recruitment and enhancing monocyte activity in a nonphlogistic manner (Rainsford 1992). Arachadonic acid-derived lipoxins (LX), particularly LXA4, have been identified as anti-inflammatory mediators, indicating that the LOX pathway has a dual proinflammatory and anti-inflammatory function.

The NSAIDs may amplify or decrease this endogenous anti-inflammatory system. Aspirin is more COX-1 selective and can impair many components of mucosal defense and enhance leukocyte adherence within the gastric and mesenteric microcirculation (Wallace & Fiorucci 2003). However, with chronic use of aspirin, there is an adaptation of the gastric mucosa that is associated with a marked upregulation of COX-2 expression and lipoxin production. This lipoxin is specifically termed aspirin-triggered lipoxin (ATL). Aspirin is unique among current therapies because it acetylates COX-2, thereby enabling the biosynthesis of 15(R)-hydroxyeicosatetraenoic acid (15(R)-HETE) from arachidonic acid, which is subsequently converted to ATL by 5-LOX. Inhibition of either the COX-2 or 5-LOX enzymes results in blockade of ATL synthesis (Wallace

& Fiorucci 2003). Lipoxin A4 and ATL (a carbon-15 epimer of LX) attenuate aspirin-induced leukocyte adherence, whereas administration of selective COX-2 inhibitors blocks ATL synthesis and has been shown to augment aspirin-induced damage and leukocyte adherence to the endothelium of mesenteric venules in rats (Wallace & Fiorucci 2003).

In addition to the lipoxins, aspirin-induced COX-2 acetylation results in the generation of numerous other endogenous autacoids derived from dietary omega-3 fatty acids (Serhan et al. 2002). Some of these local autacoids are potent inhibitors of neutrophil recruitment, thereby limiting the role of these cells during the resolution phase of inflammation, and thus are referred to as "resolvins" (Serhan et al. 2002). The identification of both the lipoxins and the resolvins has introduced new potential therapeutic avenues for the treatment of inflammation, cardiovascular disease, and cancer.

Other Pharmacologic Considerations for NSAID Use

Because of their high protein binding, NSAIDs can displace other drugs from their plasma protein binding sites and potentially increase their plasma concentration. This is rarely a concern unless administered to animals with organ dysfunction or in those receiving other highly protein bound medications with a narrow therapeutic index. Interference with the metabolism and excretion of certain coadministered drugs may occur; therefore, verifying the safety of combination therapy is always mandatory.

Some NSAIDs may induce the syndrome of inappropriate secretion of antidiuretic hormone (ADH). Renal water reabsorption depends on the action of ADH mediated by cyclic adenosine monophosphate (cAMP). As PGs exert a controlled negative feedback action on cAMP production, inhibition of PG synthesis results in above-normal levels of cAMP with potential for enhanced ADH activity. In addition, the administration of a COX-2 selective NSAID may enhance sodium and water reabsorption. Clinically, both mechanisms may result in high specific gravity urine with dilutional hyponatremia. Urine volume may be decreased through this mechanism but without renal injury (Dunn & Buckley 1986; Petersson et al. 1987).

Contraindications for NSAIDs

NSAIDs should not be administered to animals with acute renal insufficiency, hepatic insufficiency, dehydration, hypotension, conditions associated with low "effective circulating volume" (i.e., congestive heart failure and ascites), coagulopathies (i.e., factor deficiencies, thrombocytopenia, and von Willebrand's disease), or evidence of gastric ulceration (i.e., vomiting with or without the presence of "coffee ground material," and melena). Administration of NSAIDs following gastrointestinal surgery must be determined by the health of this organ at the time of surgery. As the COX-2 isoenzyme is important for healing, intuitively, NSAIDs would be contraindicated where compromised bowel is noted. Concurrent use of other NSAIDs (i.e., aspirin) or corticosteroids is not recommended. The COX-1 preferential NSAIDs are contraindicated in animals with spinal injury (including herniated intervertebral disc) due to the potential for hemorrhage and neurologic deterioration, and due to excessive bleeding at the surgical site should surgical treatment be pursued. The NSAIDs should never be administered to animals in shock, trauma cases at the time of presentation, or animals with evidence of hemorrhage (i.e., epistaxis, hemangiosarcoma, and head trauma). Animals with severe or poorly controlled asthma, or other types of moderate to severe pulmonary disease, may deteriorate with NSAID administration. Aspirin has been documented to exacerbate asthma in human patients; however, COX-2 specific NSAIDs did not result in worsening of clinical signs (West & Fernandez 2003). It is not known whether animals may be affected in this way. Although administration of NSAIDs in head trauma, pulmonary diseases, or thrombocytopenia is generally contraindicated, COX-2 preferential NSAIDs (i.e., meloxicam, etodolac, carprofen, tolfenamic acid, and deracoxib) may prove to be safe with further study. Due to inhibition of PG activity, the NSAIDs may be detrimental to reproductive function. Indomethacin may block prostaglandin activity in pregnant women, resulting in cessation of labor, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation (DuBois et al. 1998). These effects may occur in animals; therefore, NSAIDs should not be administered during pregnancy. As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo (DuBois et al. 1998), NSAIDs should also be avoided in breeding females during this stage of the reproductive cycle. As previously mentioned, the COX-2 isoenzyme is required for maturation of the embryological kidney so administration to lactating mothers should be avoided.

NSAIDs used in Veterinary Medicine

There is little data regarding clinical pharmacology of NSAIDs in exotic species, thus care must be taken when extrapolating from common domestic species.

Meloxicam Meloxicam is a COX-2 preferential NSAID approved for use in dogs in Australasia, Europe, and North America. The parenteral formulation is approved for cats in the United States and Australasia. Its use in cats in Canada is under investigation with completed studies indicating safety and efficacy. Its use in horses is also under investigation, with pharmacokinetic studies indicating that the half-life is shorter and clearance greater than in the dog, suggesting that dosing more than once a day may be necessary (Sinclair et al. 2003).

Studies indicate no renal or hepatic abnormalities with acute administration and minimal to no antithromboxane activity, suggesting hemostasis in normal animals may not be a problem (Mathews et al. 1999; Poulsen Nautrep & Justus 1999). Few adverse reactions have been documented, and most involve the gastrointestinal tract. A recent study showed no difference in gastric erosions over saline placebo when meloxicam was administered at 0.1 mg/kg for 3 days postelectrical stimulation (i.e., surgical simulation) under anesthesia. However, corticosteroids plus meloxicam in this study resulted in significant gastric erosions (Boston et al. 2003). A case report of combination aspirin and meloxicam in a dog resulted in duodenal perforation (Reed 2002). This case illustrates the importance of COX-2 in intestinal protection when aspirin is coadministered, and reinforces that different NSAIDs should not be administered concurrently. Analgesia is excellent when meloxicam is combined with an opioid.

Carprofen Although classified as a NSAID, carprofen administration to beagle dogs did not inhibit PGE_2, 12-hydroxyeicosatetrenoic acid or thromboxane B_2 synthesis in an experimental study utilizing subcutaneous tissue cage fluids (McKellar et al. 1994a). It was concluded that the principle mode of action of carprofen must be by mechanisms other than cyclooxygenase or 12-lipoxygenase inhibition. However, more recent studies indicate that it is a COX-2 preferential NSAID (Kay-Mugford et al. 2000; Ricketts et al. 1998). Carprofen is approved for perioperative and chronic pain management in dogs in Australasia, Europe, and North America. Carprofen is approved for single dose, perioperative use in cats in Europe, and is licensed for use in horses in the United Kingdom. In sheep, carprofen (0.7 mg/kg, IV) resulted in plasma concentrations of 1.5 μg/mL, similar to those required to confer analgesia in horses, for up to 48 hours (Welsh et al. 1992). However, analgesia was not assessed in this sheep study (Welsh et al. 1992). Antithromboxane activity is minimal, suggesting that induced coagulopathy may not be a problem in animals with intact hemostatic mechanisms (McKellar et al. 1990; Poulsen Nautrep & Justus 1999).

Ketoprofen Ketoprofen is approved for postoperative and chronic pain in both dogs and cats in Europe and Canada. Ketoprofen is also approved for use in horses and ruminants. As ketoprofen is an inhibitor of both COX-1 and COX-2, adverse effects are a potential problem requiring careful patient selection. Although several studies using ketoprofen preoperatively indicate its effectiveness in controlling postoperative pain, a general consensus among veterinarians has restricted its use primarily to the postoperative period to reduce the potential for hemorrhage (Lobetti & Joubert 2000; Mathews et al. 1999; Pibarot et al. 1997). Ketoprofen should not be administered to patients with risk factors for hemorrhage. It is often administered to animals immediately after orthopedic procedures (i.e., fracture repair, cruciate repair, and onychectomy).

Etodolac Etodolac is COX-2 preferential and is approved in the United States for use in dogs for the management of pain and inflammation associated with osteoarthritis, but is also useful in other painful conditions (Budsberg et al. 1999; Glaser et al. 1995). The adverse effects appear to be restricted to the gastrointestinal tract.

Deracoxib Deracoxib is a COX-2 specific inhibitor. Deracoxib is approved in the United States and Canada for control of postoperative pain and inflammation associated with orthopedic surgery in dogs. The incidence of vomiting and diarrhea were similar in dogs receiving deracoxib compared with dogs receiving placebo in a perioperative field trial, and overall the drug was well tolerated and effective (Novartis Animal Health USA 2004). It was also shown to be effective in attenuating lameness in dogs with urate crystal-induced synovitis after prophylactic and therapeutic administration (McCann et al. 2004; Millis et al. 2002). This group of NSAIDs appeared to be gastroprotective in human patients when compared with the less COX-2 specific NSAIDs, when used for 8 days to 3 months (Silverstein et al. 2000). However, more recent studies in humans indicate these NSAIDs cannot guarantee gastroprotection with chronic use. Furthermore, in a recent canine study comparing the gastrointestinal safety profile of licofelone (a dual inhibitor) to rofecoxib (another specific COX-2 inhibitor), rofecoxib, was found to induce significant gastric and gastroduodenal lesions (Moreau et al. 2005).

Diclofenac Diclofenac is available worldwide as several different human and veterinary formulations. It is a useful antiinflamatory and analgesic drug and has been studied for antimicrobial activity (Dutta et al. 2007). Diclofenac has been observed to cause severe hepatic and nephrotoxicity in many species of birds and its use, or accidentally ingestion from carcasses should be avoided (Hussain et al. 2008; Jain et al. 2009; Jayakumar et al. 2010; Naidoo et al. 2009; Oaks et al. 2004; Taggart et al. 2007).

Firocoxib Firocoxib is available as an oral paste and injectable for horses and as an oral formulation for dogs. The efficacy and adverse events appear similar to other coxib-class NSAIDs (Food and Drug Administration: Center for Veterinary Medicine [FDA-CVM], 2011).

Robenacoxib Robenacoxib is available (currently outside the United States) as an oral and injectable formulation for treatment of pain and inflammation in

both dogs and cats. The efficacy and adverse events appear similar to other coxib-class NSAIDs.

Mavicoxib Mavicoxib is a long-acting NSAID approved outside the United States for use in dogs. The dosing interval is usually 2 weeks between doses 1 and 2, the 4 weeks between subsequent doses. The elimination half-life in healthy dogs is approximately 2 weeks (range 7.9–38.8 days) (Cox et al. 2010). Significant individual and breed associated differences have been observed, but effects on drug safety and effectiveness have yet to be determined (Cox et al. 2011).

Tepoxalin Tepoxalin is a COX-1, COX-2, and LOX inhibitor of varying degrees with efficacy comparable with meloxicam or carprofen and safety comparable with placebo (FDA-CVM 2005). Tepoxalin has been approved for management of osteoarthritic pain in dogs. The safety profile of tepoxalin showed no difference from placebo when administered prior to a 30-minute anesthesia period and a minor surgical procedure in dogs (Kay-Mugford et al. 2004).

Tolfenamic Acid Tolfenamic acid is approved for use in cats and dogs in Europe and Canada for controlling acute postoperative and chronic pain. The dosing schedule is 3 days on and 4 days off that must be strictly adhered to. Reported adverse effects are diarrhea and occasional vomiting. Tolfenamic acid has significant anti-inflammatory and antithromboxane activity; therefore, posttraumatic and surgical hemostasis may be compromised during active bleeding after administration of this NSAID (McKellar et al. 1994b).

Flunixin Meglumine Flunixin meglumine is a COX-1 and COX-2 inhibitor and is approved for use in dogs in Europe but not North America. It is also approved for use in ruminants and horses and is commonly used for equine colic pain.

Phenylbutazone Phenylbutazone is approved for use in horses, cattle, and dogs in North America. Since safer NSAIDs are approved for dogs, phenylbutazone is not recommended for this species. In horses, there is high risk of gastric ulceration and nephrotoxicity, where signs of toxicity may progress from inappetence and depression to colic, gastrointestinal ulceration, and weight loss (Collins & Tyler 1984; MacAllister et al. 1993; Snow et al. 1981). Phenylbutazone has a prolonged elimination half-live in cattle, ranging from 30 to 82 hours (Arifah & Lees 2002; DeBacker et al. 1980).

Aspirin Aspirin is primarily a COX-1 inhibitor. It has been most commonly used as an analgesic for osteoarthritic pain in dogs. It is also available in proprietary combinations with various opioids (aspirin plus codeine or aspirin plus oxycodone) to achieve a synergistic effect for the treatment of moderate pain. It is also used as an antipyretic and anticoagulant in dogs and cats. Aspirin has also been recommended in cattle (Gingerich et al. 1975).

NSAIDs Not Approved for Use in Veterinary Medicine (Off-Label Use)

Ketorolac Ketorolac is a COX-1 and COX-2 inhibitor and is included for the benefit of those working in the research setting associated with human hospitals where the availability of ketorolac is more likely than other NSAIDs. Adverse gastrointestinal effects are common.

Acetaminophen Acetaminophen is a COX-3 inhibitor with minimal COX-1 and COX-2 effects. It should not be administered to feline species due to deficient glucuronidation of acetaminophen in these species (Court & Greenblatt 1997).

Dipyrone Dipyrone is a COX-3 inhibitor and is approved for use in cats and dogs in Europe and Canada. Dipyrone should be given intravenously to avoid the irritation experienced when given intramuscularly. The analgesia produced is not usually adequate for moderate to severe postoperative pain, and dipyrone is reserved for use as an antipyretic in cases where other NSAIDs are contraindicated. Dipyrone induces blood dyscrasias in humans; however, this has not been reported in animals.

ALPHA-2 ADRENERGIC RECEPTOR AGONISTS AND ANTAGONISTS

Introduction

The use of alpha-2 adrenergic agonists in veterinary medicine began following the synthesis of xyalazine in 1962. Early reports of the sedative and anesthetic sparing qualities of xylazine predated the elucidation of its mechanism of action in 1981. Alpha-2 adrenoreceptors have been identified in the CNS, cardiovascular, respiratory, renal, endocrine, gastrointestinal, and hemotologic systems, resulting in widespread drug effects (Aantaa et al. 1995). Most FDA-CVM approved alpha-2 agonists carry label indications as sedatives and analgesics.

Alpha-2 adrenoceptors are linked to Gi-protein second messengers (Aantaa et al. 1995). These are similar to those used by many opioid receptor subtypes and in fact, opioid and alpha-2 agonists usually have additive or synergistic effects (Maze & Tranquilli 1991). Alpha-2 adrenoreceptors are classically described as being located presynaptically at noradrenergic neurons exerting an inhibitory feed-back role on the release of subsequent norepinephrine (NE) (Maze & Tranquilli 1991). This results in decreased sympathetic nervous system efferent activity and probably is related to the decreased vigilance, decreased anesthetic requirements,

and decreased heart rate and blood pressure observed following administration of these drugs to most species. Alpha-2 adrenoreceptors are also found in the vascular smooth muscle (a nonpresynaptic site) and when activated result in vasoconstriction. This results in increased vascular resistance and will result in increased baroreceptor-mediated vagal tone. The result is slowing of heart rate and decreasing cardiac output, but blood pressure remains within physiologic normal values. Confusion often exists about the clinical effect of alpha-2 agonist administration (e.g., hypertension [postsynaptic] vs. hypotension [presynaptic]) expected in a patient. The net clinical result will vary with route of administration, dose, species, and the duration of time following the administration.

Alpha-2 agonist doses vary at least 10-fold across species. Pigs tend to have the highest requirements, followed by cats, dogs, horses, and finally ruminants. Breed and sex differences also exist within cattle that should be appreciated.

Alpha-2 Adrenergic Agonist Effects

Central Nervous System Alpha-2 adrenergic agonists exert many of their inhibitory effects on central nervous system (CNS) function through inhibiting NE release from sympathetic neurons (Maze & Tranquilli 1991). Inhibition of intraneuronal transmission is also responsible for muscle relaxation observed following alpha-2 adrenergic agonist administration. Analgesia is mediated by spinal and supraspinal alpha-2 adrenergic receptors. Agonist binding modulates afferent activity at a spinal level and increases the diffuse noxious inhibitory control system activity. The net result is sedation, reduced anesthetic requirements, reduced stress responses, and analgesia. It should be noted that alpha-2 agonists, like all sedatives and tranquilizers, are not anesthetics. Although animals can appear in a sleep-like state, they may become aroused by noxious stimulation and may become defensive. Additionally, on rare occasions, paradoxical behavior (aggression rather than sedation) may be noted. Accidental intracarotid injection of alpha-2 adrenergic agonists will induce seizure-like activity and must be avoided.

Emetic Center Alpha-2 agonists are predictable emetics in cats and dogs, especially at high doses. This is due to activation of the chemoreceptor trigger zone of the area postrema (Hikasa et al. 1992). Dopaminergic blocking agents do not prevent alpha-2-induced emesis.

Thermoregulation Alpha-2 agonists will often cause changes in thermoregulation. The effect is usually a decrease; however, increases can be seen when animals are placed in warm environments. This is especially a concern when alpha-2 agonists are used for capture of cattle or other hoof-stock. If possible, body temperature should be monitored for 12–24 hours following sedation or administration of an alpha-2 adrenergic antagonist should be considered. In smaller animals, hypothermia is more common and may be due to decreased metabolic activity accompanying sedation as well as decreased thermoregulatory control. It is usually not a life-threatening problem if managed appropriately.

Eye Alpha-2 agonists generally cause mild miosis to little change in pupil diameter and a mild decrease in intraocular pressure (IOP) (Verbruggen et al. 2000). The class of drugs is relatively contraindicated with increases in intraocular pressure or corneal lacerations because of the probability of inducing vomiting (which causes further increases in IOP) in those species that can vomit.

Respiratory System Most alpha-2 adrenergic receptor agonists can cause decreased responsiveness to CO_2, especially in higher doses. This effect is compounded by the coadministration of opioids or anesthetic agents and is of concern during anesthesia. In some species, alpha-2 agonists do not normally depress respiration to the point of creating hypoxia and cyanosis. In fact, arterial blood gas values for PaO_2 are usually normal. The bluish color of the mucous membranes that may be noticed on occasion is usually due to slowed venous blood flow accompanying vasoconstriction. As the capillary transit time increase, oxygen extraction increases, and notable hemoglobin desaturation will appear as a blue(ish) color. Oxygen therapy will often resolve this condition. However, in sheep and possibly some other species, xylazine administration has been shown to result in central hypoxemia related to pulmonary changes (Celly et al. 1997, 1999).

Cardiovascular System Intravenous administration of alpha-2 adrenergic agonists typically results in rapid and pronounced vasoconstriction (Pypendop & Verstegen 1998). If heart rate and cardiac output do not decrease (as can be seen with atropine administration), blood pressure would increase impressively (Alibhai et al. 1996; Short 1991). However, normal baroreceptor reflexes attempt to maintain blood pressure within physiologic limits by increasing vagal tone and slowing heart rate. Heart rate may decrease by 50–75% in some individuals. The cardiac rhythm is often a slow sinus rhythm characterized by two or three sequential beats followed by a long sinus pause. Occasionally, second-degree atrioventricular blockade will be seen. Both rhythms are often responsive to antimuscarinic administration (block the vagal reflex) and high heart rates (and blood pressures) will result. Intramuscular or oral administration tends to decrease the incidence of profound bradycardia.

After the initial direct vasoconstriction occurs, vasodilation and reduction in blood pressure may be seen.

This is more prominent in primate species. The alpha-2 adrenergic receptor agonists decrease sympathetic nervous system efferent activity, which results in decreased vasomotor tone and heart rate. Alpha-2 adrenergic agonists have historically been used in humans as antihypertensive agents because they reduce vasomotor tone and block the reflex increase in heart rate that can accompany alpha-1 antagonists.

Most of the contraindications to alpha-2 adrenergic receptor agonist administration are related to their cardiovascular side effects. As a general rule, this class of drugs should not be administered to animals that do not have normal healthy cardiovascular systems and/or are exercise intolerant. There are some exceptions, but a thorough understanding of the underlying disease is required and appropriate monitoring necessary.

Urinary Tract Alpha-2 adrenergic receptor agonists increase urine output by increasing production of dilute urine (Grimm et al. 2001; Saleh et al. 2005). This is primarily related to inhibition of antiduretic hormone (ADH) release and/or synthesis, as well as changes in renal hemodynamics (Saleh et al. 2005).

Gastrointestinal Tract Animals may have complications associated with decreased propulsive activity, including colic and bloat, although this is unusual in most species (Thompson et al. 1991). Longer-acting drugs are more likely to result in a problem. Patients should be observed following alpha-2 adrenergic receptor agonist administration for signs of abdominal distension.

Endocrine A classic neroendocrine response is hyperglycemia following alpha-2 agonist administration (Abdel el Motal & Sharp 1985; Osman & Nicholson 1991). This is due to a decrease in insulin release. It is usually transient and not clinically significant, although alpha-2 agonists should not be used to sedate animals for glucose curves.

Since alpha-2 agonists reduce sympathetic activity and inhibit the stress response, neuroendocrine markers of the stress response should be affected. Cortisol levels are usually decreased following alpha-2 agonist administration and may not be reliable as indicators of stress or pain (Brearley et al. 1990; Sanhouri et al. 1992).

Specific Drugs

Several alpha-2 adrenergic receptor agonists are approved for veterinary use. Generally, their pharmacologic actions will be similar, but the duration of action and species compatibility will vary. All alpha-2 agonists are potent and potentially dangerous following accidental human ingestion or injection. Care should be taken when handling syringes loaded with these drugs and medical help should be sought immediately if exposure occurs.

Xylazine Xylazine is the prototypical veterinary alpha-2 adrenergic receptor agonist. Another alpha-2 agonist, clonidine, has been used in humans as an antihypertensive agent and is often used as the prototypical drug in research applications. Xylazine has been administered to many different species, both domestic and exotic. It is readily available and relatively inexpensive.

Xylazine has a shorter duration of action than many of the other drugs. Typical doses will result in muscle relaxation and sedation of horses for 45–60 minutes. This can be advantageous when performing field anesthesia/sedation when a rapid recovery is desired. Xylazine is often combined with opioids like butorphanol to enhance sedative and analgesic qualities.

Detomidine Detomidine is a longer acting alpha-2 agonist approved for use in horses as a sedative. It is commonly administered when profound, long-lasting sedation is needed. When used in high doses as a preanesthetic, low respiratory rates may accompany induction. Detomidine is not used in small animals and has not been widely evaluated in exotic species.

Medetomidine Medetomidine is approved for use as a sedative/analgesic in dogs. The drug has also been extensively evaluated in all domestic species and many exotic and zoological species. It is extremely selective for the alpha-2 receptor and binds it avidly. Atipamezole was developed as the specific antagonist for medetomidine for this reason.

Romifidine Romifidine is an alpha-2 adrenergic receptor agonist that is approved for use in horses. It has been evaluated in other species and appears to be relatively safe, but offers few advantages over other approved products. Some equine clinicians believe is it is a good sedative without causing excessive ataxia.

Dexmedetomidine Dexmedetomidine is the newest of the alpha-2 adrenergic agonists to be marketed to veterinarians. Unlike medetomidine, which is a racemic mixture of two stereoisomers, dexmedetomidine contains only the pure dextrorotatory enantiomer, which appears to be responsible for all of the clinically relevant properties of the drug. Due to the absence of the inactive levorotatory enantiomer, dexmedetomidine is twice as potent as medetomidine. It is currently marketed as a solution with half the strength of medetomidine, meaning that equivalent doses of dexmedetomidine and medetomidine have the same volume. The sedative, analgesic, and anesthetic-sparing effects of both drugs appear to be similar when administered at equivalent doses in dogs and cats (Ansah et al. 1998; Granholm et al. 2006, 2007; Kuusela et al. 2000). Hemodynamic side effects also appear similar. While it has been proposed that recoveries from dexmedetomidine

may be faster compared with medetomidine due to the additional metabolic burden imposed by levomedetomidine, there is no current evidence to support this claim.

Alpha-2 Adrenergic Receptor Antagonists

One big advantage alpha-2 adrenoreceptor agonists have over other sedative/tranquilizers like acepromazine is reversibility. It is possible to administer an antagonist and within minutes animals will regain function and be able to be released. Antagonist administration will usually result in opposite hemodynamic effects (e.g., acute vasodilation and tachycardia), and they should not be administered in a cavalier fashion. Many of the difficulties (including some deaths) occur with reversal. Also, alpha-2 agonist-mediated analgesia is reversed, necessitating administration of other analgesic classes to animals in pain. Some species (e.g., domestic horses) are not routinely reversed because of the potential for uncontrollable activity and possible self-trauma.

Yohimbine Yohimbine is a plant-derived compound that has been used by humans for centuries because of its performance enhancing properties. It is relatively effective for reversing xylazine in horses, dogs, and cats, but is less effective in ruminants. Additionally, yohimbine has some stimulant actions that may result in excitation upon recovery. Yohimbine has not been effective at reversing newer agents like medetomidine.

Tolazoline Tolazoline was originally used as a therapy for human infants suffering from pulmonary hypertension. It is a relatively nonselective alpha-receptor blocker and is useful for reducing pulmonary vascular resistance. It is also effective at antagonizing xylazine sedation. It is most commonly used for equine and ruminant species. It appears more effective in ruminant species than yohimbine.

Atipamezole Atipamezole is the marketed antagonist for medetomidine and dexmedetomidine. It is effective at reversing all available alpha-2 adrenoreceptor agonists and its use is limited only by cost. It is relatively selective for alpha-2 adrenergic receptors and usually does not cause excessive stimulation, although excitation may occur. Atipamezole is approved for use in dogs; however, it is used in other species commonly. Under most circumstances, it is best given by the IM route except in emergency situations.

PHENOTHIAZINES AND BUTYROPHENONES

Introduction

The phenothiazines and butyrophenones produce an array of behavioral, autonomic, and endocrine effects and have been used clinically in numerous domestic and wild species. Their tranquilizing effects are mediated by antagonism of dopamine receptors (primarily the D2 subtype) located in the cerebral cortex, basal ganglia, and limbic system. In addition, other antidopamine effects are noted in the hypothalamus (increased prolactin secretion and impaired thermoregulation), brainstem (impaired vasomotor reflexes), and chemoreceptor trigger zone of the medulla (antiemesis). Both drug classes also have varying antagonistic effects at adrenergic (alpha-1 and alpha-2), serotonergic (5HT), muscarinic (M1), and histaminergic (H1) receptor systems. It is important to note that they do not possess any inherent analgesic properties and their effects are not reversible.

Acepromazine Acepromazine is the most widely used phenothiazine tranquilizer in veterinary medicine. In dogs and cats it is commonly combined with an opioid to produce a state historically referred to as "neuroleptanalgesia." Such combinations are suitable to provide chemical restraint for short, noninvasive procedures or as preanesthetic medication prior to induction of general anesthesia. Acepromazine administration in the preanesthetic period will cause dose-dependent reductions in both injectable and inhalant anesthetic requirements in these species. In horses and cattle, the drug is used primarily for its antianxiety effects. In susceptible pigs, acepromazine has been shown to prevent or reduce the onset of halothane-induced malignant hyperthermia. In certain wild and exotic species, the combination of acepromazine and the potent opioid etorphine (Large Animal Immobilon) has been used for immobilization and anesthesia.

Cardiovascular effects of acepromazine include decreases in mean arterial blood pressure in the range of 20–30% accompanied by dose-dependent reductions in stroke volume and cardiac output. Isoflurane, due to its potent vasodilatory effects, appears to potentiate acepromazine-induced hypotension. At clinically relevant doses, heart rate may not change appreciably or may increase slightly. At very high doses, bradycardia and sinoatrial block may occur. Acepromazine has also been shown to reduce the arrhythmogenic effects of epinephrine and halothane.

In general, effects on pulmonary function (i.e., oxygenation and ventilation) tend to be minimal in conscious animals, though respiratory rate may decrease somewhat. Acepromazine has been shown to dose-dependently decrease hematocrit by as much as 20–50% in dogs and horses due to splenic sequestration. This effect occurs within 30 minutes and appears to persist for at least 2 hours. The drug also decreases platelet aggregation but the clinical hemostatic significance of this appears minimal.

Regarding the gastrointestinal system, acepromazine has been shown to have antiemetic effects when

administered 15 minutes prior to morphine, hydromorphone, or oxymorphone. Lower esophageal sphincter tone is reduced, which may lead to an increased risk of gastric reflux, though this has not been proven. Decreased gastrointestinal motility and delayed gastric emptying have been demonstrated in horses.

Renal blood flow and glomerular filtration rate appear to be well maintained in dogs receiving acepromazine and isoflurane. In cats under halothane anesthesia, urethral pressure has been shown to decrease by 20% with acepromazine administration. There are anecdotal reports of penile prolapse/priapism in stallions. The magnitude and duration of the protrusion appear to be dose-dependent, and this side effect appears to be mediated by alpha adrenergic antagonism. Also, because of its antihistaminergic effects, acepromazine is not suitable for allergic skin-testing.

Azaperone Azaperone is classified as a butyrophenone and its only approved indication is for control of aggression associated with mixing or regrouping of swine. It is also used as a preanesthetic agent in pigs and has clinical properties and side effects similar to acepromazine. In various wild and exotic species, azaperone is used in combination with potent opioids, such as etorphine or carfentanil, to produce immobilization or anesthesia.

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