Chapter 9

Anticholinergics and Sedatives

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Introduction

Anticholinergics and sedatives are two of the most widely used—and misused—classes of anesthetic adjuncts in veterinary medicine. Anticholinergics are used perioperatively to manage bradycardia and atrioventricular (AV) block associated with surgical manipulation (oculovagal and viscerovagal reflexes) or with the administration of other anesthetic adjunctive drugs (e.g., α_2-agonists or opioids). Occasionally, they are also used to control excessive oral and airway secretions. Anticholinergics are often combined with sedatives and opioids as part of a preanesthetic combination. Intraoperatively, anticholinergics are used primarily to manage sinus bradycardia and other vagally mediated arrhythmias. Sedatives are used perioperatively to induce sedation, provide restraint, and reduce the amount of injectable and inhalational anesthetics required to induce and maintain anesthesia. Some sedatives suppress or prevent vomiting (phenothiazines and butyrophenones), others provide muscle relaxation (benzodiazepines), and still others provide analgesia and muscle relaxation (α_2-agonists). Sedatives can also be used to promote a smooth recovery from anesthesia, and some sedatives (α_2-agonists, opioids, and benzodiazepines) have specific antagonists that can be administered after short diagnostic and minor surgical procedures.

Anticholinergics and sedatives should not be administered perioperatively on an indiscriminate basis. Rather, the risks and benefits associated with administration of different drugs should be assessed, and the safest drugs chosen for each patient. Most injectable and inhalational anesthetics that are used currently do not cause the dramatic autonomic responses (salivation and bradycardia) that occurred with some older anesthetics (ether). Further, the tachycardia induced by anticholinergic administration may be contraindicated in some patients with cardiovascular disease (e.g., hypertrophic cardiomyopathy). Therefore, anticholinergics should be administered only when there is a clear indication for their use (prevention or treatment of bradycardia). Similarly, most sedatives have significant cardiovascular side effects. The phenothiazines can contribute to the development of significant intraoperative hypotension. The α_2-agonists consistently cause bradycardia and a decrease in cardiac output. Alternately, the benzodiazepines are relatively free of cardiovascular side effects, but may not be reliable sedatives in some patients. The following patient-related factors should be considered when selecting anticholinergics and sedatives for perioperative use: age, species, temperament, concurrent disease, medications, and previous response to anesthetic drugs. Several procedure-related factors also play a practical role in drug selection. These include the type of procedure (inpatient or outpatient, diagnostic or surgical, and elective or emergency), as well as the duration of the procedure. Availability and clinical experience with the use of anticholinergics and sedatives in different species must also be considered.

Anticholinergics

Anticholinergics are often called parasympatholytic drugs because they block the effects of the parasympathetic nervous system on other body systems—especially the cardiovascular and gastrointestinal systems. Atropine and glycopyrrolate are the anticholinergics used most commonly in veterinary medicine. These two drugs do not block nicotinic cholinergic receptors and are more accurately classified as antimuscarinics. There are three major types of muscarinic receptors: M_1, M_2, and M_3 (Table 9.1). M_1 receptors are located on neurons in the central nervous system (CNS) and on autonomic ganglia. M_2 receptors are located in the sinoatrial (SA) and AV nodes and in the atrial myocardium. M_3 receptors are located in secretory glands, vascular endothelium, and smooth muscle. The cellular response to activation of these muscarinic receptors is mediated by several different molecular mechanisms (Table 9.1). Anticholinergics can also produce indirect sympathomimetic and parasympathomimetic effects. Presynaptic muscarinic receptors (heteroceptors) located on sympathetic nerve terminals normally inhibit release of norepinephrine, and blockade of these receptors by muscarinic antagonists facilitates release of norepinephrine. Similarly, presynaptic muscarinic receptors (autoreceptors) located on parasympathetic nerve terminals normally inhibit release of acetylcholine, and blockade of these receptors by muscarinic antagonists facilitates release of acetylcholine.

Atropine and glycopyrrolate are relatively nonselective mus-

Table 9.1. Anatomical location, cellular response, and physiological response associated with different muscarinic receptor subtypes

Receptor (G Protein)	Anatomical Location	Cellular Response	Physiological Response
M_1 ($G_{q/11}$)	Neurons and autonomic ganglia	Activate PLC and increase IP_3, DAG, and cytosolic calcium	Depolarization of neurons and autonomic ganglia
M_2 ($G_{i/o}$)	Sinoatrial node, atrioventricular node, and atrial myocardium	Increase potassium conductance Inhibit AC and decrease cAMP Decrease calcium conductance	Decreased sinus rate, conduction velocity, and contractile force
M_3 ($G_{q/11}$)	Secretory glands, smooth muscle, and vascular endothelium	Activate PLC and increase IP_3, DAG, and cytosolic calcium Generation of nitric oxide	Increased secretion and smooth muscle activity, and vasodilation

AC, adenylate cylase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate; PLC, phospholipase C.

Table 9.2. Comparative effects of atropine and glycopyrrolate

	Sedation	Decrease in Oral Secretions	Increase in Heart Rate	Decrease in Gastrointestinal Motility	Ocular Effects	Increase in Gastric pH
Atropine	+	+	+++	++	++	0
Glycopyrrolate	0	++	+++	++	0	+

0, none; +, mild; ++, moderate; +++, marked.
Modified from Stoelting.[324]

carinic antagonists, but despite this lack of selectively the effectiveness of muscarinic blockade varies considerably from tissue to tissue (Table 9.2). Salivary and bronchial glands are the most sensitive to muscarinic blockade. Cardiac tissues and smooth muscle are intermediate in sensitivity, and gastric parietal cells are the least sensitive to muscarinic blockade. Cardioselective muscarinic (M_2) antagonists that prevent bradycardia and have limited effects on gastrointestinal smooth muscle activity have become available.[1,2]

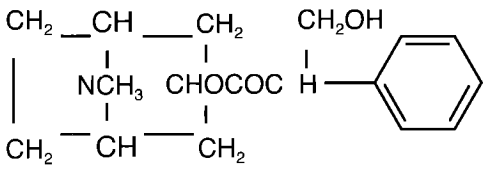
Perioperatively anticholinergics are usually administered to prevent or treat severe bradycardia caused by surgical manipulation (vagal reflexes) or by administration of other anesthetic drugs (e.g., α_2-agonists and opioids). The incidence and severity of bradyarrhythmias can be reduced by preoperative administration of atropine or glycopyrrolate, but significant arrhythmias can still occur, and anticholinergic administration should never be used as a substitute for diligent patient monitoring. Anticholinergic administration routinely causes sinus tachycardia, which is problematic for many patients with cardiovascular disease. Tachycardia associated with administration of anticholinergics leads to an increase in myocardial work and a decrease in myocardial perfusion. Further, coadministration of anticholinergics and ketamine has been associated with the development of myocardial infarcts in, and the death of, young cats undergoing routine surgical procedures.[3] Anticholinergic administration also has dramatic effects on gastrointestinal function. At therapeutic doses, nonselective muscarinic antagonists like atropine and glycopyrrolate reduce lower esophageal sphincter tone and have little effect on gastric pH.[4] These two factors increase the incidence of gastroesophageal reflux and esophagitis in anesthetized dogs.[5] Perioperative administration of anticholinergics also reduces intestinal motility and can lead to gastrointestinal complications postoperatively.[6]

Atropine

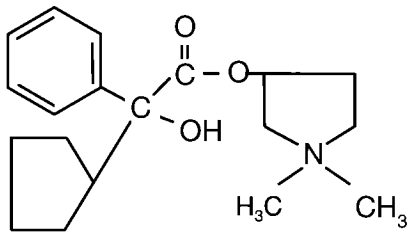
This agent is a racemic mixture of the l (−) and d (+) isomers of hyoscyamine. The l (−) isomer is at least 100 times more potent than the d (+) isomer. Chemically, atropine consists of two components (tropic acid and an organic base) that are bound by an ester linkage (Fig. 9.1). Atropine has approximately the same affinity for all three major types of muscarinic receptors. Relative to other synthetic muscarinic antagonists, atropine is very selective for muscarinic receptors and has little effect on nicotinic receptors.

Pharmacokinetics and Pharmacodynamics

Atropine is rapidly absorbed after intramuscular (IM) administration. Onset of cardiovascular effects occurs within 5 min, and peak effects occur within 10 to 20 min. After intravenous (IV) administration at a dose of 0.03 mg/kg, onset of cardiovascular effects occurs within 1 min, peak effects occur within 5 min, and heart rate increases by 30% to 40% for approximately 30 min (Fig. 9.2).[1] The effects of atropine on other body systems subside within a few hours, but ocular effects can persist for 1 to 2 days. Atropine is rapidly cleared from the blood after parenteral administration. Some of the drug is hydrolyzed to inactive metabolites (tropine and tropic acid), and some of it is excreted unchanged in the urine. Rabbits and some other species (cats and



Atropine



Glycopyrrolate

Fig. 9.1. Chemical structures of muscarinic antagonists With permission from Stoelting.[324]

rats) have a plasma enzyme (atropine esterase) that accelerates metabolism and clearance of the drug.[7]

At therapeutic doses, atropine administration produces limited effects on the CNS. A mild sedative effect may be observed, and the incidence of vomiting mediated by the vestibular system may be reduced. Blockade of the pupillary constrictor muscle and the ciliary muscle produces long-lasting mydriasis and cycloplegia, respectively. Lacrimal secretions are also reduced, which may contribute to corneal drying during anesthesia unless artificial tears are applied concurrently.[8–10] Atropine should be used with discretion in animals with acute glaucoma and increased intraocular pressure because its mydriatic effect may impede drainage from the anterior chamber.

Atropine administration produces very dramatic effects on heart rate and rhythm.[11–13] The SA and AV nodes and the atrial myocardium all receive vagal parasympathetic input. Muscarinic receptors are located both presynaptically and postsynaptically in the SA and AV nodes. The typical response to IV or IM administration of therapeutic doses (0.02 to 0.04 mg/kg) of atropine is blockade of postsynaptic muscarinic receptors that leads to an increase in sinus rate, an acceleration of AV nodal conduction, and an increase in atrial contractility. At lower doses, a transient decrease in sinus rate and slowing of AV nodal conduction (AV blockade) can occur.[11,12] This response appears to be due to blockade of presynaptic muscarinic receptors that normally inhibit acetylcholine release.[14] Once postsynaptic muscarinic blockade is established, this paradoxical increase in vagal tone usually resolves.

Airway smooth muscle and secretory glands also receive parasympathetic input from the vagus nerves. Blockade of M_3 receptors by therapeutic doses of atropine decreases airway secretions and increases airway diameter and anatomical dead space. In the past, atropine was given before administration of noxious inhaled anesthetics (ether) to reduce airway secretions and the potential for laryngospasm. Modern inhaled anesthetics do not cause the same degree of airway irritation, and routine preoperative administration of atropine for this reason is difficult to justify.

Atropine administration also produces very dramatic effects on the gastrointestinal system. Blockade of M_1 and M_3 receptors in the gastrointestinal tract reduces secretory activity and motility. In dogs, administration of atropine reduces smooth muscle contractile activity, and administration of selective M_2 antagonists has limited effects on intestinal motility.[1] Atropine is not usually administered perioperatively to large animals. Although it can be given to horses intraoperatively to manage severe bradycardia associated with administration of α_2-agonists, gastrointestinal motility is reduced and colic can occur postoperatively.[6,15]

Clinical Uses

Atropine can be given subcutaneously (SC), IM, or IV, but the IM and IV routes are preferred because uptake from subcutaneous sites can be erratic in patients with altered hydration and peripheral

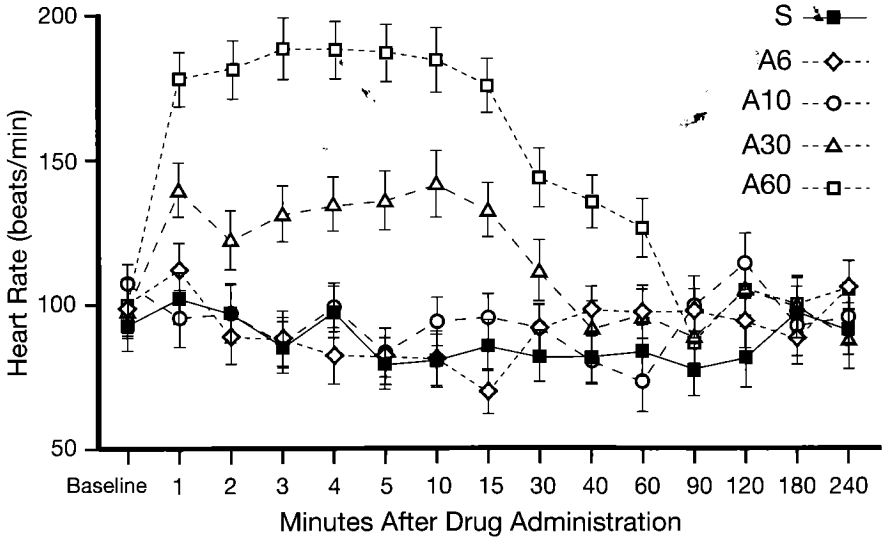


Fig. 9.2. Effect of intravenous administration of atropine (6 to 60 μg/kg) on heart rate in dogs. With permission from Hendrix and Robinson.[1]

circulation. Doses for dogs and cats range from 0.02 to 0.04 mg/kg. Atropine is also effective when given endotracheally or endobronchially to dogs for cardiopulmonary resuscitation.[16] Doses for ruminants and swine range from 0.04 to 0.08 mg/kg, but salivation may not be completed obtunded in these species. Atropine is not usually given perioperatively to horses because of its gastrointestinal side effects. Atropine can also be used to control muscarinic side effects when anticholinesterases (e.g., edrophonium) are administered to reverse neuromuscular blockade produced by nondepolarizing muscle relaxants (e.g., atracurium).

Glycopyrrolate

This is a synthetic quaternary ammonium muscarinic antagonist. Like atropine, the drug consists of two components (mandelic acid and an organic base) bound together by an ester linkage (Fig. 9.1). Glycopyrrolate is four times as potent as atropine and has approximately the same affinity for all three major types of muscarinic receptors. The drug's polar structure (quaternary amine) limits diffusion across lipid membranes and into the CNS and fetal circulation.[17]

Pharmacokinetics and Pharmacodynamics

Absorption, metabolism, and elimination of glycopyrrolate are similar to that of atropine. Absorption is rapid after IM administration. Onset of cardiovascular effects occurs within 5 min, peak effects occur within 20 min, and heart rate remains elevated for approximately 1 h.[18] Glycopyrrolate is rapidly cleared from the blood after parenteral administration, and most of the drug is excreted unchanged in the urine.

At therapeutic doses, glycopyrrolate produces few, if any, effects on the CNS. Unlike atropine administration, sedation is not observed, and recovery times are not prolonged. Administration of glycopyrrolate to conscious dogs with normal intraocular pressure does not alter pupil diameter and intraocular pressure, and intraoperative administration of glycopyrrolate to dogs with glaucoma and increased intraocular pressure appears to be safe.[19] Similarly, pupil diameter and light reflexes are unaffected when conscious horses are administered glycopyrrolate IV.[20]

Glycopyrrolate administration produces effects on the heart that are comparable to those of atropine.[12] Studies in people suggest that glycopyrrolate produces less tachycardia than atropine, but the two drugs produce similar increases in heart rate when administered IV to sedated or anesthetized dogs.[12,21] The typical response to IV or IM administration of therapeutic doses (5 to 10 μg/kg) of glycopyrrolate is an increase in sinus rate, acceleration of AV nodal conduction, and an increase in atrial contractility. At lower doses, a transient decrease in sinus rate and slowing of AV nodal conduction can occur.[12] Glycopyrrolate can also be given intraoperatively to correct bradycardia in both small and large animals. Dogs weighing less than 10 kg require a higher dose of glycopyrrolate (10 μg/kg IV) to correct bradycardia, and those over 10 kg require a lower dose (5 μg/kg IV).[22] Glycopyrrolate is given to horses at a lower dose (2.5 to 5.0 μg/kg IV) to correct bradycardia and to increase cardiac output and blood pressure (Fig. 9.3), but the potential for postoperative gastrointestinal complications (colic) must be considered.[23,24]

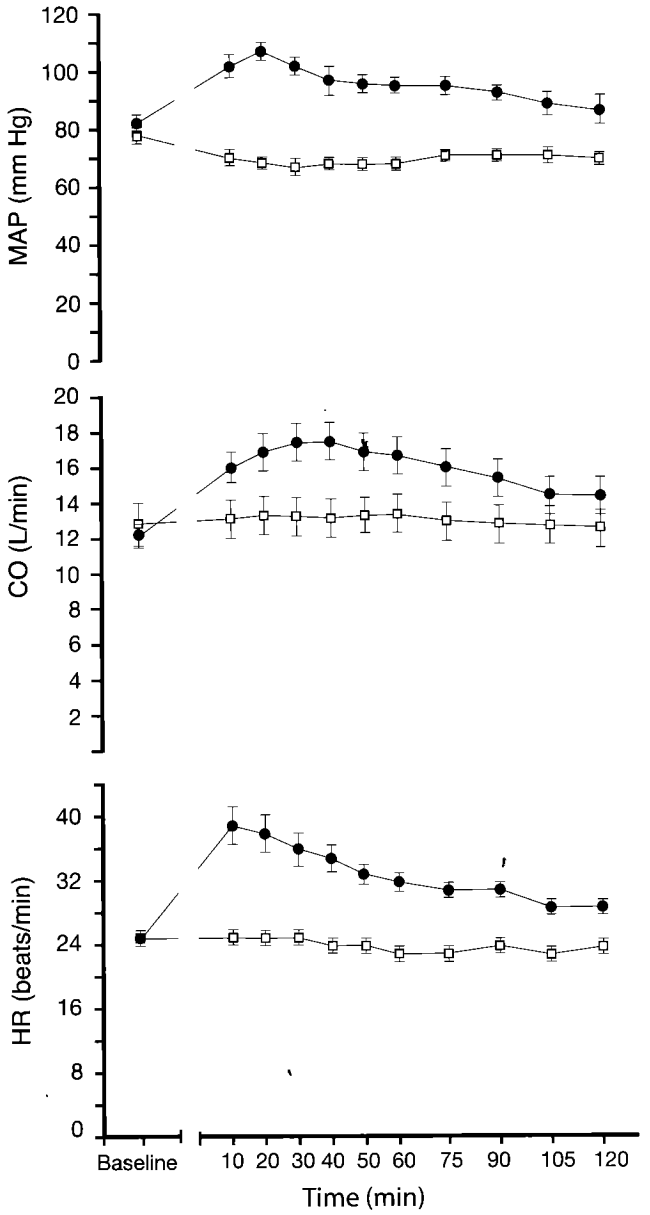


Fig. 9.3. Effect of intravenous administration of glycopyrrolate (2.5 to 7.5 μg/kg) on heart rate (HR), cardiac output (CO), and mean arterial blood pressure (MAP) in horses anesthetized with halothane and xylazine. With permission from Teixeira Neto et al.[24]

Like atropine, glycopyrrolate produces dramatic effects on the gastrointestinal system. Intestinal motility is reduced for at least 30 min in anesthetized dogs.[21] In conscious horses, gastrointestinal motility is reduced for 2.4 and 6.4 h after IV administration of glycopyrrolate at doses of 2.5 and 5.0 μg/kg, respectively.[20] Further, when these doses were given intraoperatively to 17 horses undergoing routine surgical procedures, only one horse developed signs of colic postoperatively.[23] Although well-controlled comparative studies are lacking, glycopyrrolate appears to be a safer choice than atropine for the treatment of intraoperative bradycardia in horses.

Clinical Uses

Glycopyrrolate is used perioperatively to prevent severe bradycardia caused by surgical manipulation (vagal reflexes) or by administration of other anesthetic drugs (α_2-agonists and opioids). Glycopyrrolate can be given subcutaneously (SC), IM, or IV, but the IM and IV routes are preferred because uptake from SC sites can be erratic in patients with altered hydration and peripheral circulation. Doses for dogs and cats range from 5 to 10 μg/kg. Intravenous doses for horses range from 2.5 to 5.0 μg/kg, but gastrointestinal side effects can occur. Like atropine, glycopyrrolate can be used to control muscarinic side effects when anticholinesterases (e.g., edrophonium) are given to reverse neuromuscular blockade produced by nondepolarizing muscle relaxants (e.g., atracurium).

Sedatives

Behavioral responses to different classes of sedatives vary considerably among species. The phenothiazines and α_2-agonists are effective sedatives in dogs and cats but are not reliable sedatives in swine. Conversely, the benzodiazepines are effective sedatives in ferrets, rabbits, swine, and birds but are not reliable sedatives in cats and young dogs. Dose requirements also vary considerably among species. For example, the α_2-agonists are effective sedatives in horses and cattle, but the xylazine dose requirement for horses is approximately ten times that for cattle. Because of this variability, accurate classification of these drugs as tranquillizers, sedatives, or hypnotics is problematic. Therefore, the drugs discussed in this chapter are simply referred to as sedatives, with the knowledge that their effects will vary with species and with dose.

In North America, only a limited number of sedatives are approved for use in animals. All of these sedatives are classified as phenothiazines (acepromazine), butyrophenones (azaperone), or α_2-agonists (xylazine, medetomidine, detomidine, and romifidine). Despite the widespread use of benzodiazepines (diazepam and midazolam) as sedatives, muscle relaxants, and anticonvulsants in veterinary medicine, none are approved and marketed for use in animals. In the United States, the benzodiazepine zolazepam is available in combination with a dissociative anesthetic (tiletamine) and is approved for use in cats and dogs as an anesthetic. Only acepromazine and xylazine are approved for use in cats, dogs, and horses. Medetomidine is approved for use in dogs, detomidine and romifidine are approved for use in horses, and azaperone is approved for use in swine. In Canada, acepromazine and xylazine are also approved for use in ruminants.

Selection of sedatives for different species and for animals with different behavioral and medical problems can be difficult without a thorough understanding of the physiological effects of the different classes of sedatives. In cats and dogs, administration of acepromazine or an α_2-agonist is associated with significant cardiovascular side effects (hypotension or bradycardia, respectively). Therefore, these sedatives are probably best reserved for use in young healthy animals. If a sedative is needed for pediatric, geriatric, or sick patients, administration of diazepam or midazolam should be considered. In horses, acepromazine and the α_2-agonists are the only reliable sedatives, and doses must be carefully individualized for each patient. Although midazolam is not widely used in animals, it is an excellent sedative for swine and some exotic species (rabbits, ferrets, and birds).

Phenothiazines and Butyrophenones

Phenothiazines and, to a lesser extent, butyrophenones produce a wide variety of behavioral, autonomic, and endocrine effects. The behavioral effects of these drugs are mediated primarily by blockade of dopamine receptors in the basal ganglia and limbic system. At therapeutic doses, phenothiazines and butyrophenones inhibit conditioned avoidance behavior and decrease spontaneous motor activity. At higher doses, extrapyramidal effects (tremor, rigidity, and catalepsy) can occur. These sedatives also have significant binding affinity for autonomic (adrenergic and muscarinic) and other types of receptors (Tables 9.3 and 9.4). For example, phenothiazines bind with greater affinity to α_1 recep-

Table 9.3. Relative receptor-binding affinities of phenothiazines and butyrophenones

	D_1	D_2	α_1	5-HT_2	M_3	H_1
Phenothiazines	+	++	+++	+++	+	+
Butyrophenones	++	+++	+	+	+	+

α_1, alpha receptor; D, dopamine receptor; H, histamine receptor; 5-HT_2, 5-hydroxytryptamine (serotonin) receptor; M_3, muscarinic receptor; +, weak; ++, moderate; +++, strong.

Table 9.4. Adverse effects of phenothiazines and butyrophenones

	Pharmacological Effects	Mechanism
Central nervous system	Catalepsy, tremor, and rigidity	Dopaminergic blockade
	Seizure activity	Electroencephalographic slowing and synchronization
Autonomic nervous system	Decreased blood pressure and hematocrit	α-Adrenergic blockade
	Decreased glandular secretions	Muscarinic blockade
Endocrine system	Galactorrhea, abnormal cycles, and altered libido	Dopaminergic blockade and increased prolactin secretion

tors than to dopaminergic receptors. Blockade of α_1 receptors is responsible for the hypotension that is typically associated with perioperative use of these drugs. Blockade of these receptors may also be responsible for the ability of phenothiazines and butyrophenones to protect against the development of malignant hyperthermia in susceptible animals anesthetized with halothane.[25] Dopamine receptors in the hypothalamus are responsible for tonic inhibition of prolactin secretion. Blockade of these receptors increases prolactin secretion and is responsible for most of the endocrine effects associated with administration of these drugs. Blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla produces an antiemetic effect, and depletion of catecholamines in the thermoregulatory center of the hypothalamus leads to a loss of thermoregulatory control. Phenothiazines and butyrophenones also produce slowing and synchronization of the electroencephalogram, which can facilitate the development of seizures in predisposed animals.[26]

Dopamine is largely an inhibitory neurotransmitter and is responsible for regulation of behavior, fine motor control, and prolactin secretion. Dopamine receptors are G-protein–coupled receptors and are divided into two major families of receptors: Dopamine 1 (D_1) receptors are located postsynaptically, and dopamine 2 (D_2) receptors are located both presynaptically and postsynaptically. Activation of the D_1 family of receptors increases adenylate cyclase activity and intracellular levels of cyclic adenosine monophosphate (cAMP). Activation of the D_2 family of receptors decreases adenylate cyclase activity and intracellular levels of cAMP, and can also activate other presynaptic signal transduction pathways (decrease calcium conductance) and postsynaptic signal transduction pathways (increase potassium conductance). Most behavioral effects are mediated by the D_2 family of receptors.

Acepromazine

This is one of the most widely used sedatives in veterinary medicine. The chemical name of acepromazine is 2-acetyl-10-(3-dimethylaminopropyl) phenothiazine (Fig. 9.4). The drug is more potent than other phenothiazine derivatives and produces sedation at relatively low doses. Acepromazine administration produces some muscle relaxation but has no analgesic effect. In North America, the drug is sold as acepromazine maleate and is approved for use in both small and large animals.

Pharmacokinetics and Pharmacodynamics Onset of sedation after parenteral administration of acepromazine to cats, dogs, and horses is relatively slow, and sedation persists for several hours. In dogs given acepromazine and an opioid IM, onset of sedation is observed within 15 min, peak effects are observed within 30 min, and sedation lasts for 2 to 3 h.[27,28] In horses given acepromazine IV, peak effects are observed within 30 min and sedation lasts for 1 to 2 h.[29,30] The pharmacokinetics of IV administration of acepromazine have been determined in horses at relatively high doses. At a dose of 0.3 mg/kg, acepromazine is widely distributed (V_d = 6.6 L/kg), is extensively protein bound (>99%), and has an elimination half-life of 3 h.[29] At a dose of 0.15 mg/kg, acepromazine has a smaller volume of distribution (V_d = 4.5 L/kg) and shorter elimination half-life (1.6 h).[30] The drug is metabolized by the liver, and unconjugated and conjugated metabolites are excreted in the urine.[31]

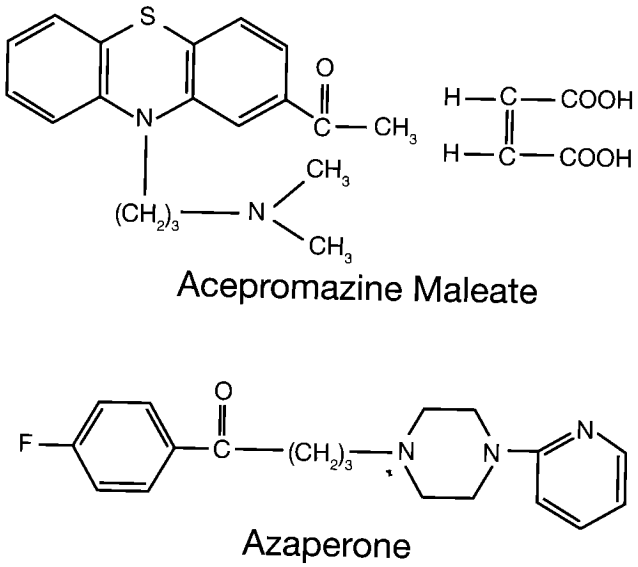


Fig. 9.4. Chemical structures of acepromazine and azaperone. With permission from Gross.[325]

Acepromazine administration decreases halothane and isoflurane requirements in several species. In dogs anesthetized with halothane, IM administration of acepromazine at doses of 0.02 and 0.2 mg/kg decreases the minimum alveolar concentration (MAC) by 34% and 44%, respectively.[32] In a comparative study, IM administration of acepromazine (0.2 mg/kg) to dogs anesthetized with halothane or isoflurane decreased the MAC by 28% and 48%, respectively.[33] Administration of acepromazine (0.05 mg/kg IV) also decreases the MAC of halothane in ponies by 37% and the MAC of isoflurane in goats by 44%.[34,35] Given the 30% to 40% reduction in halothane and isoflurane requirements that occurs when acepromazine is given perioperatively, patients should always be monitored closely and vaporizer settings reduced accordingly.[36]

Acepromazine administration produces dramatic effects on the cardiovascular system in both conscious and anesthetized animals. In conscious dogs, stroke volume, cardiac output, and mean arterial pressure decrease 20% to 25% after IV administration of acepromazine (0.1 mg/kg), and mean arterial pressure is reduced for at least 2 h.[37,38] In conscious cats, IM administration of acepromazine (0.1 mg/kg) decreases mean arterial pressure by 30% within 10 min of injection.[39] In dogs anesthetized with halothane, IV administration of acepromazine at doses of 0.05, 0.125, and 0.25 mg/kg decreases mean arterial pressure by 2.3%, 9.4%, and 16.8%, respectively.[40] Preanesthetic administration of acepromazine (0.1 mg/kg IM) also decreases mean arterial pressure by 24% in dogs anesthetized with isoflurane (Fig. 9.5).[41] In conscious horses, administration of acepromazine (0.1 mg/kg IV) decreases mean aortic pressure by 20% to 30% and decreases cardiac output by 10% to 15%.[42] In horses anesthetized with

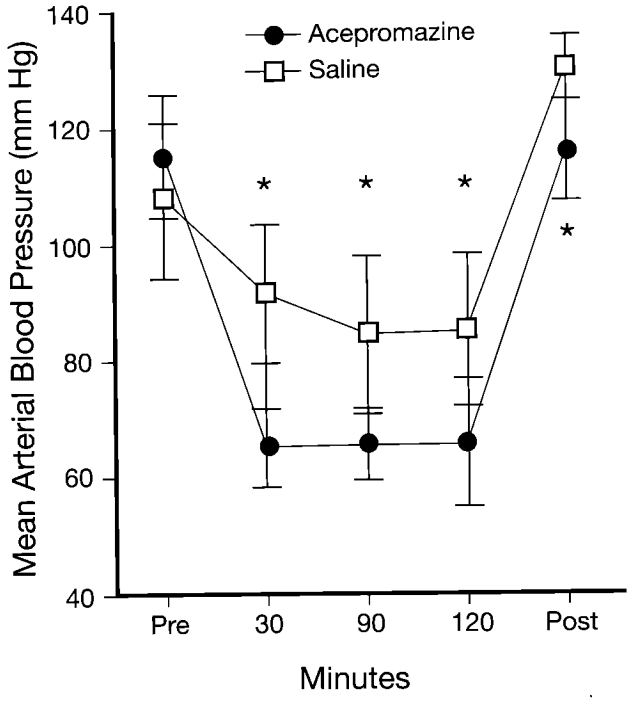


Fig. 9.5. Effect of acepromazine (0.1 mg/kg intramuscularly) on mean arterial pressure in dogs anesthetized with isoflurane (2%). With permission from Bostrom et al.[41]

halothane, IV administration of acepromazine (0.03 mg/kg) decreases mean arterial pressure by 25%.[43] When acepromazine is given preoperatively to animals anesthetized with halothane, a modest decrease in arterial pressure occurs. However, when acepromazine is given to animals anesthetized with isoflurane, a dramatic decrease in arterial pressure occurs. Currently, the widespread practice of administering acepromazine preoperatively, maintaining anesthesia with isoflurane, and failing to monitor arterial pressure contributes to the high incidence of intraoperative hypotension in small animals.

Heart rate does not change appreciably in conscious dogs and horses administered acepromazine (0.1 mg/kg IV).[37,42] Increases in heart rate and sinus tachycardia can occur in some patients. At very high doses (1 mg/kg), bradycardia and SA block can occur in dogs given acepromazine, but these arrhythmias are not usually observed at lower doses.[44] Heart rate decreases after administration of acepromazine in dogs anesthetized with halothane but does not change in horses anesthetized with halothane.[43,45] Premedication with acepromazine also increases the dose of epinephrine required to induce ventricular arrhythmias in dogs anesthetized with halothane.[46,47] Blockade of myocardial α_1 receptors by acepromazine may prevent the development of ventricular arrhythmias in anesthetized animals—provided that adequate diastolic pressure is maintained.[48]

Administration of acepromazine to conscious or anesthetized animals has little effect on pulmonary function. In conscious dogs and horses, respiratory rate decreases, but arterial pH, partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), and hemoglobin saturation do not change after IV administration of acepromazine.[42,44] In horses anesthetized with halothane, respiratory rate and arterial blood-gas values do not change after IV administration of acepromazine.[43]

Acepromazine administration produces significant gastrointestinal and urogenital effects. In dogs, administration of acepromazine 15 min before administration of morphine, hydromorphone, or oxymorphone lowers the incidence of vomiting from 45% to 18%.[49] However, administration of acepromazine alone or in combination with an opioid reduces lower esophageal sphincter tone, delays gastric emptying, and may increase the incidence of gastric reflux.[50–52] In horses, acepromazine administration delays gastric emptying and reduces intestinal motility.[53,54] Glomerular filtration is maintained in dogs premedicated with acepromazine and anesthetized with isoflurane.[41] Acepromazine also decreases urethral pressure by 20% in cats already anesthetized with halothane.[55]

Acepromazine administration can produce significant hematologic side effects in animals. In dogs and horses, hematocrit decreases by 20% to 30% within 30 min of acepromazine administration and remains well below baseline values for at least 2 h.[29,30,56] Acepromazine administration also inhibits platelet aggregation but does not appear to alter hemostasis in normal dogs.[57] Bradycardia and hypotension can occur in boxers and other breeds of dogs after acepromazine administration. These animals usually respond to fluid loading with isotonic crystalloids and administration of an anticholinergic to correct the bradycardia. Acepromazine administration produces penile protrusion in horses, and both the degree and duration of protrusion are dose dependent.[29] At a dose of 0.04 mg/kg, protrusion is 60% of the maximum length within 30 min and is below 30% after 90 min. At a dose of 0.4 mg/kg, protrusion is over 90% of the maximum length within 30 min and is still over 80% after 4 h. Although uncommon, prolonged prolapse or priapism can occur, and amputation may be required.[58] Low doses of acepromazine can be used safely in geldings but should be avoided in breeding stallions.

Clinical Uses Clinical uses of acepromazine are usually restricted to healthy animals. The drug is administered alone as a sedative for nonpainful diagnostic procedures or in combination with an opioid for painful diagnostic and minor surgical procedures. Acepromazine is also given alone and in combination with opioids as a preanesthetic to facilitate placement of IV catheters and to reduce the dose of injectable and inhalational anesthetics required to induce and maintain anesthesia. Small doses of acepromazine can also be given postoperatively to smooth recovery—provided that patients are hemodynamically stable and that pain has been managed effectively. Administration of acepromazine postoperatively to quiet patients in the absence of effective analgesic therapy makes accurate assessment of pain impossible and is inhumane. The drug is used in several species, including cats, dogs, and horses, but is not a reliable sedative in swine. Acepromazine can be given SC, IM, or IV, but the IM and IV routes are preferred because uptake from SC sites can be erratic in patients with altered peripheral circulation. Intramuscular

doses for cats and small dogs range from 0.05 to 0.2 mg/kg, and those for larger dogs range from 0.04 to 0.06 mg/kg. Intravenous doses for horses range from 0.02 to 0.04 mg/kg.

Azaperone

This agent is a butyrophenone derivative (Fig. 9.4). The chemical name of the drug is 4-fluoro-4-(4-[2-pyridyl]-1-piperazinyl) butyrophenone. In North America, azaperone is approved for use in swine to produce sedation and control aggression when groups of animals are mixed. The drug produces some muscle relaxation but has no analgesic effect. Like acepromazine, azaperone can be used alone or in combination with other drugs (e.g., opioids and ketamine).

Pharmacokinetics and Pharmacodynamics In pigs, sedation begins within 10 min after IM administration of azaperone at the label dose (2 mg/kg). Ideally, animals should be left undisturbed in a quiet environment for approximately 20 min. Peak sedation is reached within 15 min in young pigs and within 30 min in mature animals, and sedation persists for 2 to 3 h. Excitement has been observed in other species when azaperone is administered IV.[59] Limited pharmacokinetic data are available for azaperone, but the drug is metabolized by the liver and is rapidly cleared from tissues.

Azaperone administration produces dramatic effects on the cardiovascular system. Heart rate and cardiac output decrease by 20% to 40% in young pigs given azaperone IM at a dose of 2.5 mg/kg.[60] Arterial pressure decreases in pigs given azaperone IM at doses ranging from 0.3 to 3.5 mg/kg, and the pressure decrease is not dose dependent.[61]

As with acepromazine, azaperone administration has little effect on pulmonary function, but thermoregulation is impaired. Small increases in respiratory rate and decreases in arterial PCO_2 occur in pigs given azaperone IM at doses of 1 to 3.5 mg/kg.[61] Rectal temperature decreases 1° to 2°C over 4 h after IM administration of azaperone at a dose of 5 mg/kg.[62] Intramuscular administration of azaperone at a low dose (0.5 mg/kg) prevents serious fighting in breeding boars, but penile prolapse occurs in a small percentage of animals (<4%).[60]

Clinical Uses Clinical uses of azaperone are usually restricted to healthy swine. The drug is used alone as a sedative for nonpainful diagnostic procedures or in combination with an opioid for painful diagnostic and minor surgical procedures. Azaperone is also used alone and in combination with opioids as a preanesthetic to facilitate placement of IV catheters and to reduce the dose of injectable and inhalational anesthetics. Intramuscular administration of azaperone at a dose of 1 to 2 mg/kg produces a mild to moderate sedative effect in most swine. Azaperone is also given in combination with ketamine to immobilize or anesthetize animals for various diagnostic and surgical procedures. In swine, administration of azaperone (1 mg/kg IM) and ketamine (5 to 10 mg/kg IM) will immobilize most animals, and administration of azaperone and ketamine at twice these doses will anesthetize most animals. Injections should always be made with needles long enough to reach the target muscle groups. In small pigs, 1-inch needles are adequate, but longer needles must be used in mature animals. In Canada, animals given azaperone must not be slaughtered for food for at least 1 day.

α_2-Agonists

α_2-Agonists are the most widely used class of sedatives in veterinary medicine. In most species, these drugs induce reliable dose-dependent sedation, analgesia, and muscle relaxation that can be readily reversed by administration of selective antagonists.

Xylazine has been used in both small and large animals for over two decades, and detomidine has been used in horses for over a decade.[63,64] In small animals, medetomidine has been used for several years in North America and in Europe.[65–67] Romifidine has also been used in horses in North America and in Europe.[64] Selective antagonists (tolazoline, yohimbine, and atipamezole) are available for use in both small and large animals in several countries. α_2-Agonists and their antagonists are also used to facilitate capture and handling of many exotic species.[68,69]

The α_2 receptors are located in tissues throughout the body, and norepinephrine is the endogenous ligand for these receptors. The α_2 receptors exist presynaptically and postsynaptically in neuronal and nonneuronal tissues, and extrasynaptically in the vascular endothelium and in platelets. Within the nervous system, α_2 receptors are located presynaptically on noradrenergic neurons (autoreceptors) and on nonnoradrenergic neurons (heteroceptors). The sedative and anxiolytic effects of α_2-agonists are mediated by activation of supraspinal autoreceptors or postsynaptic receptors located in the pons (locus ceruleus), and the analgesic effects are mediated by activation of heteroceptors located in the dorsal horn of the spinal cord.[70] Supraspinal α_2 receptors located in the pons also play a prominent role in descending modulation of nociceptive input.

Three distinct α_2-receptor subtypes (A, B, and C) have been identified.[71–73] The cellular response to activation of these receptor subtypes is mediated by several different molecular mechanisms (Table 9.5). Physiological responses have been determined in transgenic or "knockout" animals, but specific cellular responses associated with each of the receptor subtypes have not been clearly defined. The α_{2A} receptors mediate sedation, supraspinal analgesia, and centrally mediated bradycardia and hypotension, whereas the α_{2B} receptors mediate the initial surge in vascular resistance and reflex bradycardia. The α_{2C} receptors mediate the hypothermia that accompanies administration of α_2-agonists. Neurotransmitter release is modulated primarily by presynaptic α_{2A} receptors, and spinal analgesia appears to be mediated by both α_{2B} and α_{2C} receptors. Subtype selective agonists are not currently available, but α_{2A} selective agonists with fewer vascular side effects could potentially be developed.

In contrast to the physiological effects mediated by α_2 receptors, activation of α_1 receptors produces arousal, excitement, and increased locomotor activity in animals.[74,75] These behaviors are also observed after administration of excessive doses of less selective α_2-agonists and after accidental intracarotid injection. Excitement and muscle rigidity occur in dogs administered xylazine IM at high doses (4 to 8 mg/kg).[76] Similarly, excitement,

Table 9.5. Anatomical location, cellular response, and physiological response associated with different α_2-receptor subtypes

Receptor (G Protein)	Anatomical Location	Cellular Response	Physiological Response
α_{2A} ($G_{i/o}$)	Cerebral cortex, locus caeruleus, and platelets	Inhibit AC activity and decrease cAMP Increase potassium conductance Decrease calcium conductance	Sedation and supraspinal analgesia Centrally mediated bradycardia and hypotension
α_{2B} ($G_{i/o}$)	Spinal cord (dorsal root ganglia) and vascular endothelium	Activate PLC and increase IP_3, DAG, and cytosolic calcium	Spinal analgesia Vasoconstriction and peripherally mediated reflex bradycardia
α_{2C} ($G_{i/o}$)	Spinal cord (dorsal root ganglia)		Spinal analgesia Hypothermia and modulation of dopaminergic activity

AC, adenylate cylase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate; PLC, phospholipase C.

seizures, and muscle rigidity occur in horses after intracarotid injection of xylazine.[77] This paradoxical response appears to be more common after administration of α_2-agonists that have some affinity for α_1 receptors (xylazine), but can occur in animals given toxic doses of more selective agonists.[78] Activation of central α_1 receptors can also antagonize the sedative effects of selective α_2-agonists.[79,80] Receptor binding or selectivity ratios (α_2/α_1) for xylazine, detomidine, romifidine and medetomidine are 160:1, 260:1, 340:1, and 1620:1, respectively.[81,82]

As with acepromazine, the clinical use of α_2-agonists is usually restricted to healthy animals. α_2-Agonists can be used alone or in combination with opioids to provide sedation for diagnostic and minor surgical procedures. α_2-Agonists can also be used in combination with ketamine to provide anesthesia for brief surgical procedures. Perioperatively, α_2-agonists are used at lower doses, alone or in combination with opioids, to produce sedation and analgesia required for catheter placement, to reduce the amount of injectable anesthetic (e.g., ketamine, thiopental, or propofol) required to induce anesthesia, and to reduce the amount of inhalational anesthetic (e.g., halothane or isoflurane) required to maintain anesthesia.[67] α_2-Agonists also potentiate the effects of other analgesic drugs (opioids and local anesthetics) and attenuate the stress response associated with surgical trauma. Postoperatively, low doses of α_2-agonists can be used to facilitate recovery from anesthesia in both small and large animals.

In small animals, the perioperative use of α_2-agonists has been controversial.[83,84] Certainly, the initial vasoconstriction and reflex bradycardia induced by administration of α_2-agonists are problematic. However, at low doses, these cardiovascular effects are not as pronounced nor as long in duration and are well tolerated by healthy animals. Preoperatively, anticholinergics can be administered with α_2-agonists to prevent bradycardia. α_2-Agonists also dramatically reduce the amount of thiopental or propofol required to induce anesthesia, and the amount of isoflurane required to maintain anesthesia.[85–87] Given that all of these anesthetics have a very narrow therapeutic range and produce dramatic effects on myocardial function, the reduction in dose achieved by administering α_2-agonists preoperatively significantly reduces the adverse cardiovascular effects associated with administration of most general anesthetics. Isoflurane administration also produces marked vasodilation and significant reductions in arterial pressure at concentrations normally required to induce and maintain anesthesia.[88] In dogs, concurrent administration of α_2-agonists initially increases vascular tone and attenuates the vasodilation and reduction in arterial pressure induced by high concentrations of isoflurane.[89,90] As a result, perioperative administration of α_2-agonists attenuates the vasodilatory effects of isoflurane by enhancing vascular tone. In sharp contrast, administration of acepromazine exacerbates vasodilation and the reduction in arterial pressure induced by isoflurane (Fig. 9.5).[41]

Some patients may be refractory to the sedative effects of α_2-agonists. Failure to achieve optimal sedation with α_2-agonists is often due to preexisting stress, fear, excitement, and pain. All of these conditions increase endogenous catecholamine levels and can interfere with reductions in excitatory neurotransmitter release induced by administration of α_2-agonists. Sedation is consistently achieved when xylazine or another α_2-agonist is given to calm patients in quiet surroundings with minimal environmental stimuli. In most species, sedation is even more reliable when α_2-agonists are administered in combination with opioids.

Concerns have been raised about the potential for α_2-agonists to sensitize the myocardium to epinephrine-induced arrhythmias.[48] Initial studies reported that high doses of xylazine facilitate the development of reentrant ventricular arrhythmias (premature depolarizations and tachycardia) in dogs anesthetized with thiopental and halothane—two drugs that dramatically sensitize the myocardium to epinephrine.[46,91] Subsequent studies in dogs anesthetized with halothane or isoflurane and administered lower doses of xylazine or medetomidine showed that α_2-agonists do not facilitate the development of reentrant ventricular arrhythmias.[47,92–94] Further, the decrease in sympathetic tone and increase in parasympathetic tone induced by the administration of selective α_2-agonists appear to attenuate the development of epinephrine-induced arrhythmias in dogs.[95]

In a 1998 survey of veterinarians in Ontario, an increase in the incidence of anesthetic complications was associated with the use of xylazine in small animals.[96] Failure to appreciate the dra-

matic reduction in anesthetic requirements produced by preoperative administration of xylazine and subsequent administration of a relative overdose of injectable or inhalational anesthetic may have contributed to the increased risk reported in this study. Given that patient monitoring standards were extremely lax a decade ago, failure to recognize and treat significant bradyarrhythmias could have been a factor, as well. More recent studies have found that administration of relatively low doses of medetomidine alone or in combination with opioids is associated with occasional bradyarrhythmias (sinus bradycardia and AV block) and a low incidence of severe anesthetic complications. Glycopyrrolate administration decreases the incidence and severity of bradyarrhythmias in healthy older (≥5 years old) dogs given medetomidine and butorphanol IM as preanesthetics, and only 1 of 88 dogs developed complications severe enough to require reversal with atipamezole.[97] Similarly, no anesthetic deaths and only 13 protocol modifications were recorded after repeated sedation of 136 geriatric cats (1862 procedures) and 541 geriatric dogs (6329 procedures) with medetomidine, butorphanol, and glycopyrrolate to facilitate radiation therapy.[98] Based on the latter studies, it appears that low doses of α_2-agonists can be used safely in older dogs and cats, provided that cardiopulmonary function is evaluated carefully before drug administration and monitored closely afterward.

Xylazine

Although its mechanism of action was unknown at the time of its introduction into clinical practice, xylazine was the first α_2-agonist to be used by veterinarians. The drug was synthesized in West Germany in 1962 for use as an antihypertensive in people but was found to have potent sedative effects in animals. The chemical name for xylazine is 2(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine hydrochloride (Fig. 9.6). Initially, the drug was used as a sedative in cattle and other ruminants in Europe. In the early 1970s, reports of xylazine's utility as an anesthetic adjunct began appearing in American and European veterinary literature.[99–109] These reports documented the effectiveness of xylazine in eliminating muscular hypertonicity in dogs and cats given ketamine, and in producing rapid, predictable sedation, analgesia, and muscle relaxation in horses and cattle after IV administration. It was also evident that there was tremendous variation in the dose of xylazine required to produce equivalent levels of sedation and analgesia in different species. In 1981, the sedative and analgesic effects of xylazine were definitively linked to activation of central α_2-adrenergic receptors.[110,111]

Pharmacokinetics The pharmacokinetics of xylazine have been determined in cattle, horses, and dogs after its IV and IM injection at doses of 0.2, 0.6, and 1.4 mg/kg, respectively.[112] After IV administration, the elimination half-life is 36, 50, and 30 min in cattle, horses, and dogs, respectively. After IM administration, peak plasma concentrations are reached within 15 min, and the elimination half-life is 58 and 35 min in horses and dogs, respectively. In cattle given xylazine IM (0.35 mg/kg), the drug and its metabolites are undetectable in tissues after 3 days and in milk after 12 h.[113] Despite the rapid clearance of xylazine from tissues

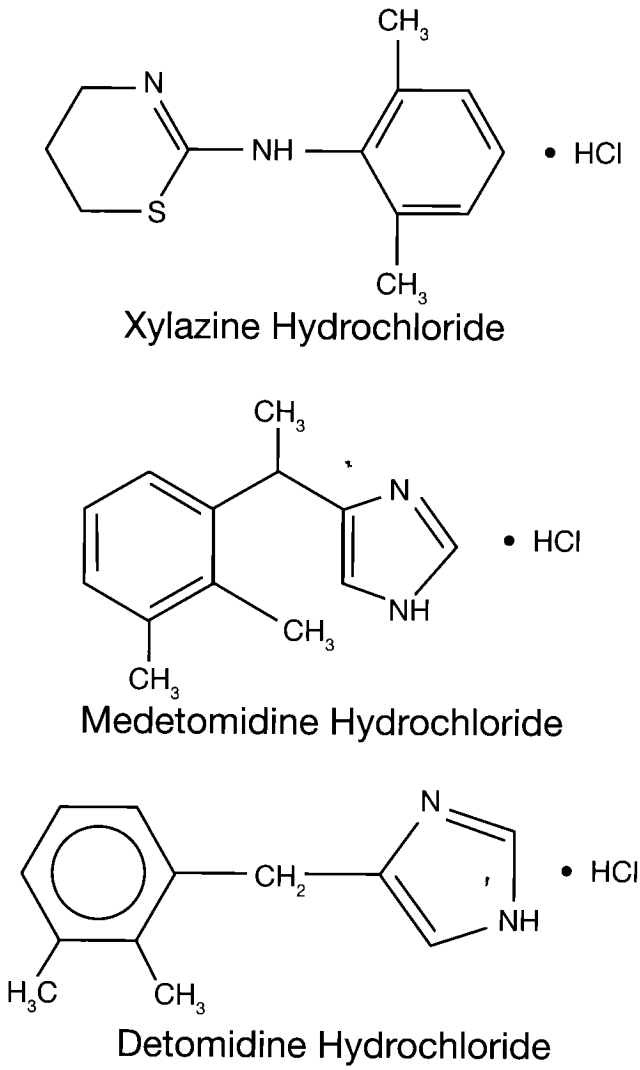


Fig. 9.6. Chemical structures of α_2-receptor agonists. With permission from Gross.[325]

and milk, the United States Food and Drug Administration has refused to approve its use in food-producing animals.[114] This refusal underscores the failure to address animal-welfare issues associated with performing surgical procedures in the absence of appropriate sedation and analgesia, and legitimate human-safety concerns associated with restraint and handling of unsedated animals. Xylazine is approved for use in ruminants in Canada and several other countries around the world.

Pharmacodynamics In most species, the onset of sedation and analgesia is rapid after parenteral administration of xylazine. In dogs, peak sedation and analgesia develop within 15 min and persist for 1 to 2 h after administration of xylazine (2.2 mg/kg IM).[115] In horses, peak sedation and analgesia develop within 5 min, persist for the next 30 min, and then subside over the next 30 min after administration of xylazine (1.1 mg/kg IV).[82,103,108,116] At a lower dose of xylazine (0.4 mg/kg IV), peak sedation develops

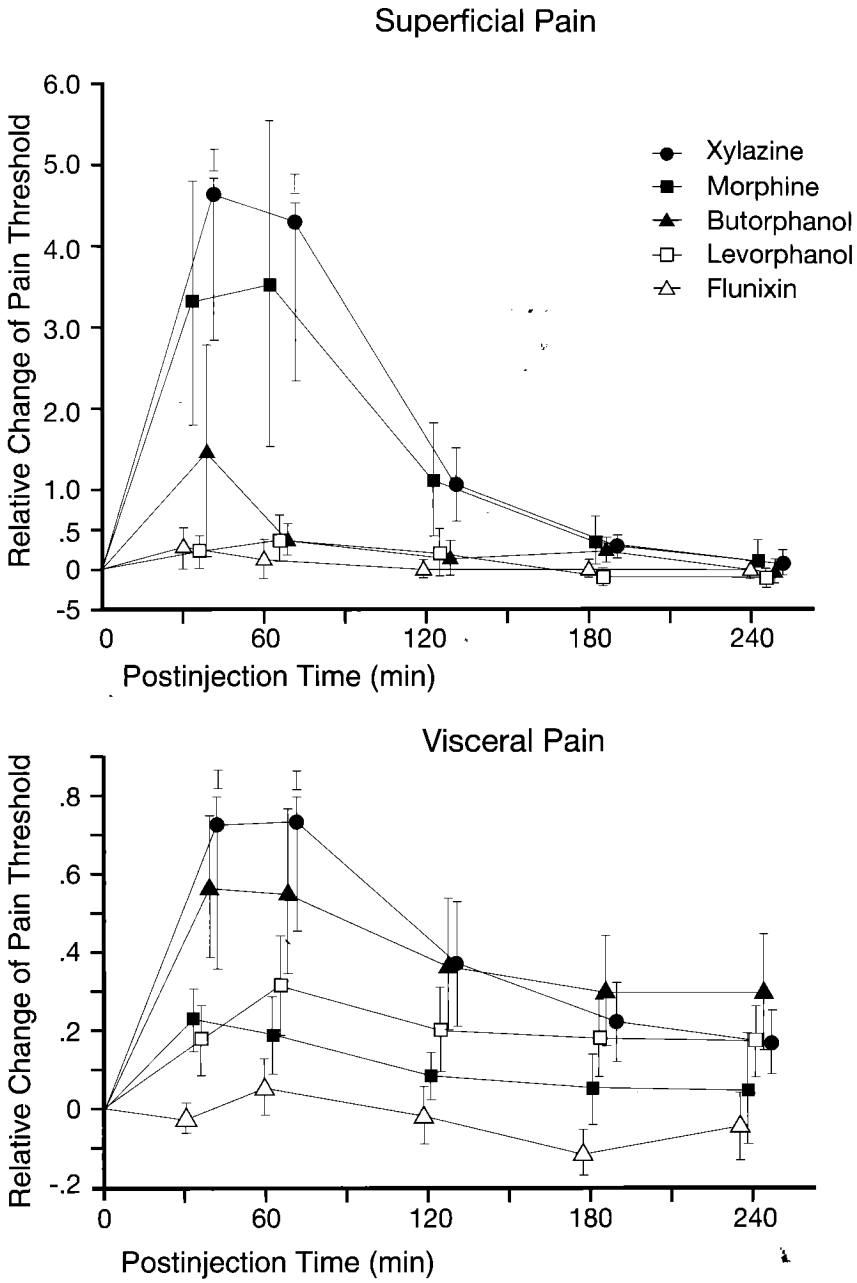


Fig. 9.7. Somatic and visceral analgesic effects of xylazine, morphine, butorphanol, levorphanol, or flunixin in ponies. With permission from Kalpravidh et al.[119]

with 10 min and then subsides over the next 20 min.[117] Most clinical studies show that the sedative and analgesic effects of xylazine are comparable in duration and do not support the "conventional wisdom" that the analgesic effect is significantly shorter than the sedative effect. Further, xylazine has been reported to be more effective than either opioid agonists (meperidine, methadone, morphine, oxymorphone, or fentanyl), agonist-antagonists (pentazocine, butorphanol, or levorphanol), or nonsteroidal anti-inflammatories (flunixin) in relieving somatic and visceral pain in horses (Fig. 9.7).[118,119]

Xylazine administration decreases injectable and inhalational anesthetic requirements dramatically in several species. Intramuscular administration of xylazine (2.2 mg/kg) decreases the dose of thiopental required to induce anesthesia in and cats and dogs by 80%.[120,121] Although this dose of xylazine is relatively high and not recommended, this study illustrates the striking reduction in thiopental requirements that can be achieved when large doses of α_2-agonists are given as preanesthetics. Similarly, administration of xylazine (0.8 mg/kg IM) decreases the dose of propofol required to induce anesthesia in dogs by over 50%.[86,122] Perioperative administration of xylazine also reduces halothane and isoflurane requirements in animals. In dogs, administration of xylazine (1.1 mg/kg IV) decreases the MAC of halothane by 38%, an effect that was reversed by administration of an α_2-antagonist (tolazoline).[123] In horses, administration of xylazine (0.5 mg/kg IV) decreases the MAC of halothane and isoflurane by 20% and 25%, respectively (Fig. 9.8).[124,125] Given the results of these studies, doses of injectable and inhalational anesthetics

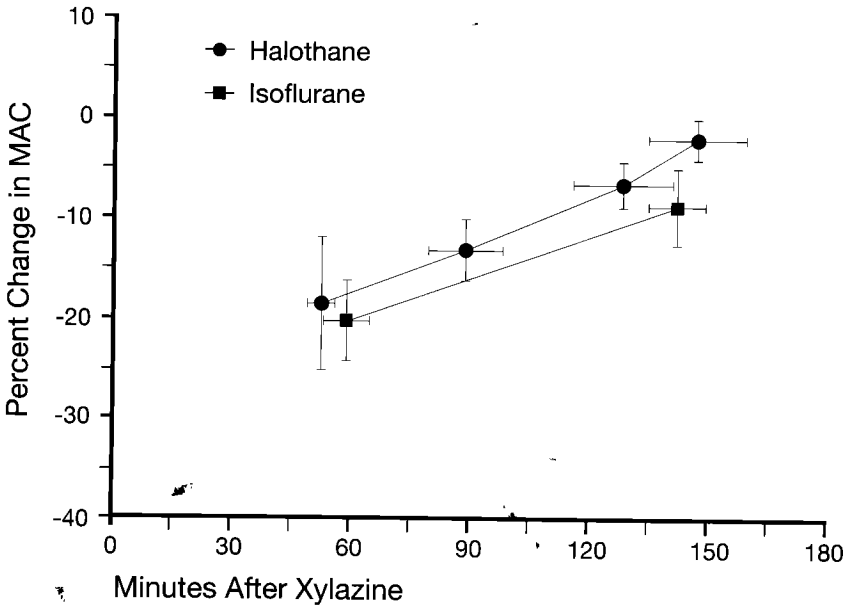


Fig. 9.8. Effects of xylazine (0.5 mg/kg intravenously) on the minimum alveolar concentration (MAC) of halothane or isoflurane in horses. With permission from Bennett et al.[124]

should be significantly reduced when xylazine is administered perioperatively to both small and large animals.

Intravenous administration of xylazine induces a brief period of hypertension and reflex bradycardia, followed by a longer-lasting decrease in cardiac output and arterial pressure. In most species, cardiac output decreases by 30% to 50% and arterial pressure by 20% to 30%.[42,103,126,127] The initial hypertensive phase is caused by activation of peripheral postsynaptic α_2 receptors, which produces vascular smooth muscle contraction and vasoconstriction. In horses, administration of a low dose of xylazine (0.4 mg/kg IV), produces less dramatic changes in arterial pressure, heart rate, and cardiac output.[117] Pretreatment with a calcium-channel blocker such as nifedipine dampens the initial increase in arterial pressure in dogs anesthetized with halothane.[128] In dogs, xylazine administration is associated with a decrease in splenic weight, which suggests a decrease in systemic vascular capacity.[129] Subsequent reductions in arterial pressure are due to decreases in sympathetic tone resulting from activation of central and peripheral (presynaptic autoreceptors) α_2 receptors. Xylazine administration also decreases heart rate by enhancing vagal tone and baroreceptor reflexes.[130] In contrast to the cardiovascular effects observed after IV injection, increases in arterial pressure and vascular resistance are not as dramatic after IM administration of xylazine in dogs and horses.[109,126] In calves given xylazine IM, hemodynamic effects are characterized by a 20% to 30% decrease in heart rate and cardiac output, and a 10% decrease in arterial pressure—without an initial increase in pressure.[131] These results suggest that IM administration of xylazine in calves does not cause transient vasoconstriction and an increase in arterial pressure to the same degree as it does in dogs and horses.

When xylazine is administered with ketamine, decreases in heart rate and cardiac output are partially offset. Ketamine administration increases heart rate and cardiac output, but arterial pressure, systemic vascular resistance, and myocardial oxygen consumption increase, as well.[127,132] Because of these acute cardiovascular changes, xylazine-ketamine combinations should be reserved for use in healthy patients and not be used in patients with myocardial disease or reduced cardiopulmonary reserve.[127,132,133]

Sinus bradycardia and AV block are the arrhythmias that are encountered most commonly after xylazine administration.[126,127] Development of these arrhythmias is a normal physiological response to the increase in vagal tone induced by xylazine. Several studies have also assessed the ability of xylazine, administered alone or in combination with other anesthetic drugs, to sensitize the myocardium to the development of epinephrine-induced arrhythmias.[48] This is usually accomplished by measuring the amount of epinephrine required to induce premature ventricular depolarizations, and this amount is called the *arrhythmogenic dose of epinephrine* (ADE). In an initial study using a more severe test (the epinephrine fibrillation threshold), premedication with xylazine decreased the dose of epinephrine required to induce fibrillation in dogs anesthetized with thiamylal and halothane, whereas premedication with acepromazine had the opposite effect.[46] In a later study, ketamine administration reportedly decreased the ADE more than did xylazine administration, and coadministration decreased the ADE more than either drug alone.[134] Studies using a saline-controlled ADE model to reduce experimental error associated with repeated epinephrine administration demonstrated no change in the ADE after IM administration of xylazine or medetomidine in dogs anesthetized with halothane or isoflurane.[92,93] From these studies, it is clear that, if anesthetic-induced changes in the ADE (arrhythmogenicity) are a concern, selection of the inhalational anesthetic (halothane vs. isoflurane) is far more critical than selection of an α_2-agonist as the preanesthetic.

Although respiratory rate decreases after administration of clinically recommended doses of xylazine, arterial pH, PO_2, and PCO_2 remain virtually unchanged in cats, dogs, and horses.[42,103,117,126,127,135] Decreases in respiration rate are ac-

companied by increases in tidal volume, which keep alveolar ventilation and arterial blood-gas values relatively constant.[127,136] In horses suffering from recurrent obstructive pulmonary disease (heaves), xylazine administration decreases pulmonary resistance, increases dynamic compliance, and may have some therapeutic value.[137] In contrast, when a large dose of xylazine (1.0 mg/kg IV) is administered to healthy dogs, minute ventilation, physiological dead space, oxygen transport, venous PO_2 and oxygen content, and oxygen consumption decrease, and tidal volume increases.[127] Xylazine administration also increases airway resistance and resonant frequency in calves.[138] Intravenous administration of xylazine to horses (0.5 to 1.0 mg/kg) and sheep (0.02 to 0.05 mg/kg) anesthetized with halothane increases airway pressure and decreases arterial PO_2.[43,139] Similarly, arterial PO_2 decreases after administration of xylazine (0.05 to 0.3 mg/kg IV) to conscious sheep.[140–142] The results of these studies suggest that the decrease in arterial PO_2 is produced by activation of peripheral α_2 receptors and a perfusion-related imbalance between ventilation and the pulmonary circulation. Additionally, the dramatic decrease in arterial PO_2 observed in sheep after administration of xylazine may be primarily caused by a pulmonary inflammatory response that is confined to ruminants with a unique population of intravascular macrophages.[143,144] Thus, although the bulk of the evidence indicates a minimal detrimental effect on respiratory function in most domestic animals, caution is advised when administering xylazine or other α_2-agonists to small ruminants, when administering high singular or cumulative doses to any species, or when combining α_2-agonists with injectable or inhalational anesthetics that produce significant cardiopulmonary depression.

Alterations in gastrointestinal function after xylazine administration have been reported in several species. Excessive salivation can occur in animals that have not been given anticholinergics. In dogs, gastroesophageal sphincter pressure decreases, which may increase the incidence of gastroesophageal reflux.[50] Most cats and 10% to 20% of dogs vomit shortly after IM administration of xylazine. Emesis may be linked to activation of central α_2 receptors because prior administration of yohimbine—but not cholinergic, dopaminergic, histaminergic, serotonergic, or opioid receptor antagonists—prevents emesis.[145] Occasionally, acute gastric distension can occur in large dogs (>25 kg) given xylazine IV or IM.[146] This distension may be caused by aerophagia or by the parasympatholytic effects of xylazine on the gastrointestinal tract, leading to atony and accumulation of gas.

Xylazine administration decreases gastrointestinal motility and prolongs gastrointestinal transit time in several species. In dogs, it decreases gastrin secretion and gastrointestinal motility, and prolongs gastrointestinal transit time.[147–149] In sheep and cattle, cyclical contractions of the reticulum and rumen are inhibited by administration of xylazine and other α_2-agonists, and administration of α_2-antagonists (tolazoline or yohimbine) antagonizes these gastrointestinal effects.[150] In horses, motility of the cecum and colon are inhibited by administration of xylazine or xylazine-butorphanol, and normal bowel myoelectrical activity returns slowly after administration of xylazine-ketamine.[151,152] However, intestinal smooth muscle relaxation and analgesia mediated by activation of central and peripheral α_2 receptors also play an important role in the relief of visceral pain.[153] Indeed, xylazine is reportedly more effective than either opioids or nonsteroidal anti-inflammatory drugs in relieving visceral pain in ponies and horses.[119,154] In addition to increasing the visceral pain threshold, xylazine administration effectively sedates and calms painful horses and helps to prevent self-induced trauma. As expected, these desirable modifications in behavior are also accompanied by a decrease in intestinal motility and blood flow. This decrease in intestinal blood flow is disproportionate to the total decrease in cardiac output, which suggests that α_2 receptors mediate vasoconstriction within the intestinal vasculature.[155] Additionally, administration of an α_2-antagonist (yohimbine) attenuates ileus and hypoperfusion associated with endoxemia in horses, which provides further evidence of the important role of α_2 receptors in the regulation of gastrointestinal function.[156]

Urine output increases after xylazine administration in cattle, horses, ponies, and cats.[157–160] Urine specific gravity and osmolality also decrease in horses and ponies.[158,159] Although urethral closure pressure decreases in both male and female dogs given xylazine, normal micturition reflexes are maintained.[161] Decreases in urethral closure pressure are coupled to a reduction in electromyographic activity of the urethral sphincter, but xylazine administration does not appear to alter the detrusor reflex in dogs.[162,163]

Transient hypoinsulinemia and hyperglycemia have been reported in several species sedated with xylazine or that are anesthetized using a regimen that incorporates xylazine.[164–169] Hyperglycemia results from α_2-receptor–mediated inhibition of insulin release from pancreatic beta cells, and the magnitude and duration of these actions appear to be dose dependent.[167] Other hormonal changes induced by xylazine include transient alterations in growth hormone, testosterone, prolactin, antidiuretic hormone, and follicle-stimulating hormone levels.

Myometrial tone and intrauterine pressure increase after xylazine administration in cattle.[170] In pregnant sheep, myometrial activity doubled for 1 h after xylazine administration, whereas fetal diaphragmatic activity is reduced.[171] In horses, administration of equipotent doses of xylazine, detomidine, or romifidine produces comparable increases in intrauterine pressure.[172] Clinically, α_2-agonists have been administered during all stages of pregnancy in several domestic species but have not been definitively associated with an increased incidence of reproductive complications.[63] α_2-Agonists also reduce cardiac output and could impair fetal oxygen delivery. Although administration of xylazine and other α_2-agonists has not been linked definitively to abortion and premature labor, the indiscriminate use of these drugs in pregnant animals during the last trimester is not advised.

Xylazine administration causes mydriasis, which may be due to either central inhibition of parasympathetic input to the iris, direct activation of α_2 receptors located in the iris, or both.[173,174] Xylazine administration also lowers intraocular pressure in rabbits, cats, and monkeys by reducing sympathetic tone and decreasing aqueous flow.[175] More importantly, administration of xylazine to dogs and cats can cause vomiting, which increases intraocular pressure dramatically.

Xylazine can also be administered epidurally to horses and cattle. In addition to an analgesic effect mediated by activation of spinal α_2 receptors (heteroceptors), xylazine has a significant membrane-stabilizing or local anesthetic effect when applied to neurons or nerve fibers. This effect is characterized by a reduction in conduction velocity and blockade of action potentials.[176] Iontophoretic application of xylazine to rat cortical neurons suppresses spontaneous firing rates, and this effect is not blocked by an α_2-antagonist.[177] The results of these studies suggest that the action of locally applied xylazine is caused in part by a local anesthetic effect.

In horses, xylazine can be administered epidurally alone or in combination with a local anesthetic. When comparing xylazine and lidocaine at equal doses and volumes in ponies, xylazine induces more profound and longer-lasting analgesia after epidural administration.[178] Analgesia induced by epidural administration of xylazine does not cause the same degree of motor nerve paralysis as that caused by administration of local anesthetics.[179] In horses, the duration of epidural analgesia can be significantly prolonged by coadministration of lidocaine and xylazine, and is not associated with enhanced neurotoxicity or dramatic changes in cardiopulmonary function.[180]

In cattle, epidural administration of xylazine produces longer-lasting analgesia than does epidurally administered lidocaine or IM administered xylazine.[181] Cardiopulmonary and GI effects of epidural administration of xylazine (0.05 mg/kg) include decreases in heart rate, respiratory rate, and rumen motility.[182] Intravenous administration of tolazoline (0.3 mg/kg) rapidly antagonizes these effects but does not alter sedative and regional analgesic effects.[182] In sheep, intrathecal administration of xylazine or clonidine produces dose-dependent analgesia of the forelimbs, and analgesia is abolished by intrathecal administration of an α_2-antagonist (idazoxan).[183] These results indicate that xylazine produces part of its analgesic effect through activation of spinal α_2 receptors. This mechanism of analgesic action is further substantiated by the prolongation of analgesia observed after coadministration of morphine and a selective α_2-agonist (medetomidine) epidurally.[184]

Clinical Uses The clinical uses of xylazine are usually restricted to healthy animals. There is considerable variation among species in the dose of xylazine required to produce an equivalent sedative effect (Table 9.6). Generally, the lowest dose that will provide the required degree of sedation is administered to limit cardiovascular side effects. Xylazine is currently approved for use as a sedative in cats, dogs, horses, deer, and elk in the United States, and for cats, dogs, horses, and cattle in Canada. Xylazine—especially the 10% (100 mg/mL) solution—should be handled carefully to avoid accidental self-administration. If the drug is absorbed through mucous membranes or administered IM, profound sedation and bradycardia can occur. Medical treatment should be sought immediately, and the package insert should be given to the attending physician.

In dogs and cats, xylazine is used alone or in combination with opioids to provide sedation and analgesia for diagnostic and minor surgical procedures. The drug is also used in combination with ketamine, ketamine-diazepam, or tiletamine-zolazepam to provide anesthesia for brief surgical procedures. As a preanesthetic, xylazine is used alone or in combination with opioids to facilitate placement of IV catheters and to decrease requirements for injectable and inhalational anesthetics. Anticholinergics (atropine and glycopyrrolate) can be administered with xylazine to prevent development of severe bradyarrhythmias perioperatively. Small doses of xylazine (0.1 mg/kg) can be administered postoperatively to smooth recovery and to potentiate the effects of other analgesic drugs (opioids), provided that patients are hemodynamically stable. Xylazine can be given IV or IM, but the IM route is preferred because cardiovascular side effects are reduced. Intramuscular doses for healthy dogs and cats range from 0.5 to 1.0 mg/kg.

In horses and cattle, xylazine is used alone or in combination with butorphanol to provide sedation and analgesia for diagnostic and surgical procedures. Xylazine can also be used as a preanesthetic before induction of anesthesia with ketamine, ketamine-diazepam, ketamine-guaifenesin, or thiopental-guaifenesin. In horses anesthetized with halothane, isoflurane, or sevoflurane, small doses of xylazine (0.1 to 0.2 mg/kg) can be given IV during the maintenance and recovery phases to reduce anesthetic requirements and smooth recovery, respectively. Xylazine can be also be used in combination with ketamine and guaifenesin for total IV anesthesia. After induction of anesthesia with xylazine and ketamine, anesthesia can be maintained with a combination of xylazine, ketamine, and guaifenesin ("triple drip") for approximately 1 h.

As a general rule, cattle usually require one-tenth of the dose of xylazine that horses require to produce an equivalent level of sedation. For sedation and analgesia alone or in combination with butorphanol, IV doses for horses range from 0.2 to 0.8 mg/kg, and those for cattle range from 0.02 to 0.08 mg/kg. As a preanesthetic before induction with an injectable anesthetic and maintenance with an inhalational anesthetic, IV doses for horses range from

Table 9.6. Xylazine doses for several domesticated species

Species	Dose
Cats	0.25–0.5 mg/kg IV
	0.5–1.0 mg/kg IM
Dogs	0.25–0.5 mg/kg IV
	0.5–1.0 mg/kg IM
Horses	0.5–1.0 mg/kg IV
	1.0–2.0 mg/kg IM
Cattle	0.05–0.1 mg/kg IV
	0.1–0.2 mg/kg IM
Sheep	0.05–0.1 mg/kg IV
	0.1–0.2 mg/kg IM
Goats	0.05–0.1 mg/kg IV
	0.1–0.2 mg/kg IM
Llama	0.1–0.2 mg/kg IV
	0.2–0.4 mg/kg IM

IM, intramuscularly; IV, intravenously.

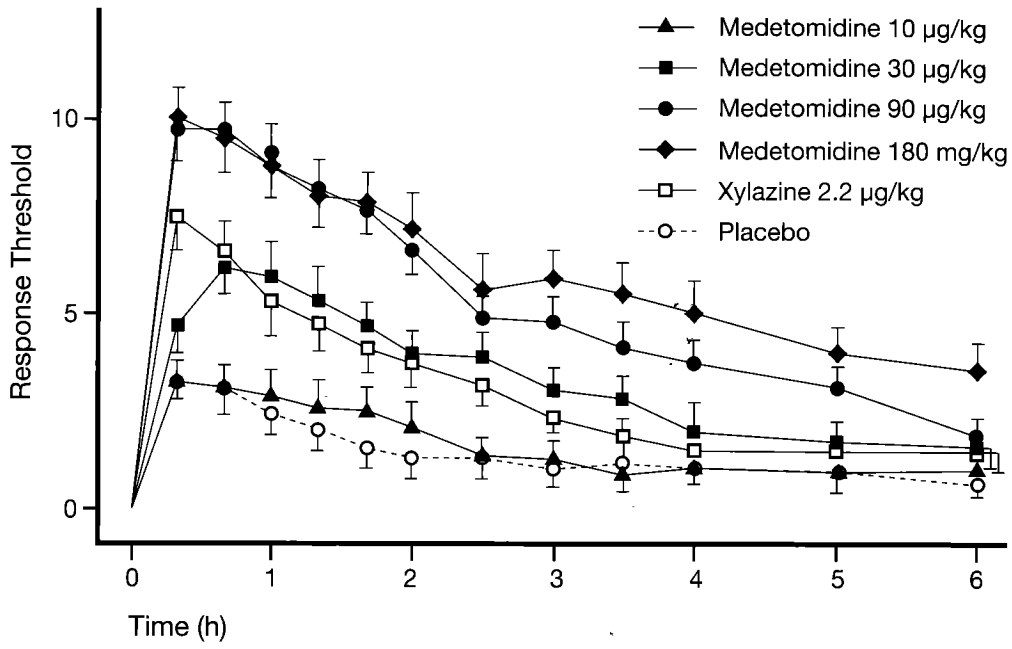


Fig. 9.9. Analgesic effects of intramuscular administration of medetomidine in dogs. Higher response threshold equates with improved analgesic action. With permission from Vainio et al.[115]

0.4 to 0.8 mg/kg, and those for cattle range from 0.04 to 0.08 mg/kg. As a preanesthetic before induction of anesthesia with ketamine or ketamine-diazepam, an IV dose of 1.0 mg/kg is typically administered to horses and a dose of 0.1 mg/kg is given to cattle. Xylazine can be administered to healthy foals and calves over 1 month of age but is not usually given to neonates. Doses of xylazine should be decreased in very large animals (draft horses and bulls) and in breeds with increased sensitivity to the drug (Brahman and Brahman crosses).[63] Xylazine doses should also be decreased in sick or debilitated animals but may need to be increased in excited animals. In horses or cattle that are fractious and difficult to restrain, xylazine can be administered IM at a dose of 1.0 to 2.0 mg/kg or 0.1 to 0.2 mg/kg, respectively.

Sudden death has been reported in horses after xylazine administration.[77] Excitement, violent seizures, and collapse can occur after accidental intracarotid injection or after IV administration of an overdose. Seizure activity that occurs immediately after intracarotid administration of xylazine is probably mediated by the activation of central α_1 receptors.[74,75] After intracarotid injection, pharmacodynamic effects extend beyond the "window of sedation" typically achieved when recommended doses of xylazine are administered IV or IM. Seizures caused by accidental intracarotid injection of xylazine can usually be controlled by IV administration of thiopental or thiopental-guaifenesin to effect. Once seizures are controlled, the horse should be intubated and supplemental oxygen administered.[63]

Medetomidine

This is the most widely used α_2-agonist in small animals. The chemical name for the drug is (±)-4-(1-[2,3-dimethylphenyl]ethyl)-1H-imidazole monohydrochloride (Fig. 9.6). It is more potent than xylazine and is dosed on a microgram-per-kilogram basis rather than a milligram-per-kilogram basis. In North America, medetomidine is approved for use in dogs as a sedative-analgesic. Studies on the sedative, analgesic, and cardiopulmonary effects of medetomidine in cats have also been reported.[185–187]

Pharmacokinetics Medetomidine is a highly selective α_2-agonist that is supplied as a racemic mixture of two optical enantiomers. Dexmedetomidine is the active enantiomer, and levomedetomidine has no apparent pharmacological activity.[188–192] Shortly after medetomidine was approved for use in dogs as a sedative-analgesic in North America, dexmedetomidine was approved for use in people as a postoperative sedative in the United States. As expected, dexmedetomidine is approximately twice as potent as the racemic mixture that is available for use in animals. In dogs and cats, medetomidine has a rapid onset of action and can be administered IV or IM. After IM administration, the drug is rapidly absorbed, and peak plasma concentrations are reached within 30 min. The elimination half-life of medetomidine (80 µg/kg) after IV and IM administration in dogs and after IM administration in cats is 0.97, 1.28, and 1.35 h, respectively.[193] At this dose, the apparent volume of distribution after IV and IM administration in dogs and after IM administration in cats is 2.8, 3.0, and 3.5 L/kg, respectively.[193] Therapeutic effects of medetomidine are terminated by removal from target tissues, which parallels clearance of the drug from plasma. Elimination occurs mainly by biotransformation in the liver, and inactive metabolites are excreted in the urine.

Pharmacodynamics Onset of sedation, analgesia, and muscle relaxation is rapid after IM administration of medetomidine to dogs and cats, and the intensity and duration of these effects depend on dose. When medetomidine is given IM to dogs at a dose of 30 µg/kg, significant sedation is apparent within 5 min and persists for 1 to 2 h.[115] Similarly, when medetomidine is given to cats at a dose of 50 µg/kg, significant sedation is apparent within 15 min and persists for 1 to 2 h.[186] At these doses, analgesia peaks within 30 min and persists for 1 to 2 h (Fig. 9.9).[115,186] In

dogs, sedation induced by IM administration of medetomidine at a dose of 30 μg/kg is comparable in intensity to that induced by IM administration of xylazine at a dose of 2.2 mg/kg but lasts longer.[115] Medetomidine has also been used as a sedative-analgesic and as a preanesthetic in horses, but, even at low doses (5 to 10 μg/kg IV), ataxia is a significant problem.[117,194,195] Sedation following IV administration of a 10-μg/kg dose of medetomidine in horses is comparable to that induced by a 1-mg/kg IV dose of xylazine.[194]

Medetomidine administration decreases injectable and inhalational anesthetic requirements dramatically in several species. Premedication with medetomidine decreases induction doses of thiopental and propofol by over 50% in dogs. Administration of medetomidine IM at doses of 10, 20, and 40 μg/kg decreases the amount of thiopental required for intubation to 7.0, 4.5, and 2.4 mg/kg, respectively.[85,196] Similarly, administration of medetomidine IM at a dose of 20 μg/kg decreases the amount of propofol required for intubation to 1.8 mg/kg.[122] Administration of medetomidine IM also appears to reduce the dose of ketamine required to induce anesthesia in dogs and cats.[197–199] Premedication with medetomidine also reduces halothane and isoflurane requirements. Administration of medetomidine IV at a dose of 10 μg/kg is reported to decrease the MAC of halothane by 90%.[200] In contrast, administration of medetomidine IV at a dose of 30 μg/kg decreased the MAC of isoflurane by only 47%.[87] Additionally, administration of medetomidine IM at a dose of 8 μg/kg consistently reduced the bispectral index value (an index of anesthetic depth) in dogs anesthetized with isoflurane (1.0, 1.5, and 2.0 MAC).[201]

As with other α_2-agonists, medetomidine administration produces dose-dependent changes in cardiovascular function.[202] Cardiovascular effects are best described in two phases: an initial peripheral phase characterized by vasoconstriction, increased blood pressure, and reflex bradycardia; and a subsequent central phase characterized by decreased sympathetic tone, heart rate, and blood pressure. Occasionally, AV blockade occurs secondary to the initial increase in blood pressure, and reflex (baroreceptors) increase in vagal tone. In conscious dogs, mean arterial pressure increases transiently, and heart rate and cardiac index decrease by approximately 60% after IV administration of medetomidine at doses ranging from 5 to 20 μg/kg.[202] At these doses, changes in mean arterial pressure, central venous pressure, and vascular resistance are dose dependent, whereas changes in heart rate and cardiac index are not. In conscious cats, mean arterial pressure does not appear to change, and heart rate and cardiac index decrease by approximately 50% after IM administration of medetomidine at a dose of 20 μg/kg (Fig. 9.10).[187] In conscious horses, IV administration of a low dose of medetomidine (4 μg/kg) produces less dramatic changes in arterial pressure, heart rate, and cardiac output.[117] In cats anesthetized with isoflurane (2%), mean arterial pressure increases from 77 to 122 mm Hg, heart rate decreases from 150 to 125 beats/min, and mean arterial flow decreases from 578 to 325 mL/min, 20 min after the IM administration of medetomidine at a dose of 10 μg/kg.[203] As with xylazine, cardiovascular responses to medetomidine administration appear to be attenuated in animals anesthetized with isoflurane.[89,90] Cerebral vasodilation is attenuated by the IV administration of low doses of dexmedetomidine (0.5, 1.0, and 2.0 μg/kg) in dogs anesthetized with isoflurane or sevoflurane (0.5, 1.0, and 1.5 MAC).[204] In dogs anesthetized with isoflurane for ovariohysterectomy, heart rate is lower but blood pressure better maintained with medetomidine premedication (20 μg/kg IM) when compared with acepromazine premedication (0.05 mg/kg IM) (Fig. 9.11).[205] In conscious animals, the decrease in cardiac output is caused primarily by the decrease in heart rate and increase in vascular resistance, and not by a direct depression of myocardial contractility.[206,207] Peripheral cardiovascular effects are most pronounced when α_2-agonists are administered IV at high doses, and these effects can be reduced by administering α_2-agonists IM at low doses.[126,208] Although cardiac output decreases after medetomidine or dexmedetomidine administration, blood flow to the heart, brain, and kidneys is maintained by redistribution of flow from less vital organs and tissues.[209]

Medetomidine administration has little effect on pulmonary function. Respiratory rate and minute ventilation decrease after medetomidine administration, but this decrease in minute ventilation appears to coincide with a decrease in carbon dioxide production, and arterial blood-gas values do not change. In conscious dogs, IV administration of medetomidine (5 to 10 μg/kg) decreases the neurorespiratory response (ventilatory drive) to increases in inspired carbon dioxide.[210] In another study in conscious dogs and cats, IM administration of medetomidine at doses of 40 and 20 μg/kg, respectively, does not alter arterial pH, PCO_2, and PO_2.[187,211] Similarly, IV administration of medetomidine (4 μg/kg) does not alter arterial pH, PCO_2, and PO_2 in conscious horses.[117] The IV administration of medetomidine (20 μg/kg) or dexmedetomidine (3 μg/kg) does not alter arterial blood-gas values and produces less depression of ventilatory drive than does isoflurane (1 MAC) in dogs.[212,213] Parenteral administration of a low dose of dexmedetomidine (0.5 μg/kg) also appears to protect against bronchoconstriction induced by nebulization of histamine in dogs anesthetized with thiopental.[214]

Medetomidine administration has significant effects on gastrointestinal function in animals. Vomiting occurs in 10% of dogs and over 50% of cats administered medetomidine IM at mean doses of 40 and 80 μg/kg, respectively.[185] Normally, this is not a problem and can be advantageous if owners or hospital staff fail to withhold food from patients before induction of anesthesia. However, the potential for development of aspiration pneumonia exists if a properly inflated, cuffed endotracheal tube is not in place. Vomiting also dramatically increases intraocular pressure, which is a potential problem for some patients with ocular injury or disease. Medetomidine administration decreases gastrin release and intestinal and colonic motility in dogs.[149,215] These effects are mediated by activation of visceral α_2 receptors and inhibition of acetylcholine release.

Medetomidine administration has significant effects on renal and urogenital function in animals. In dogs, administration of medetomidine (10 to 20 μg/kg IV) decreases urine specific gravity and increases urine production for approximately 4 h.[216] Apparently, α_2-agonists interfere with the action of antidiuretic hormone on the renal tubules and collecting ducts, which increases the production of dilute urine.[217,218] Activation of α_1 re-

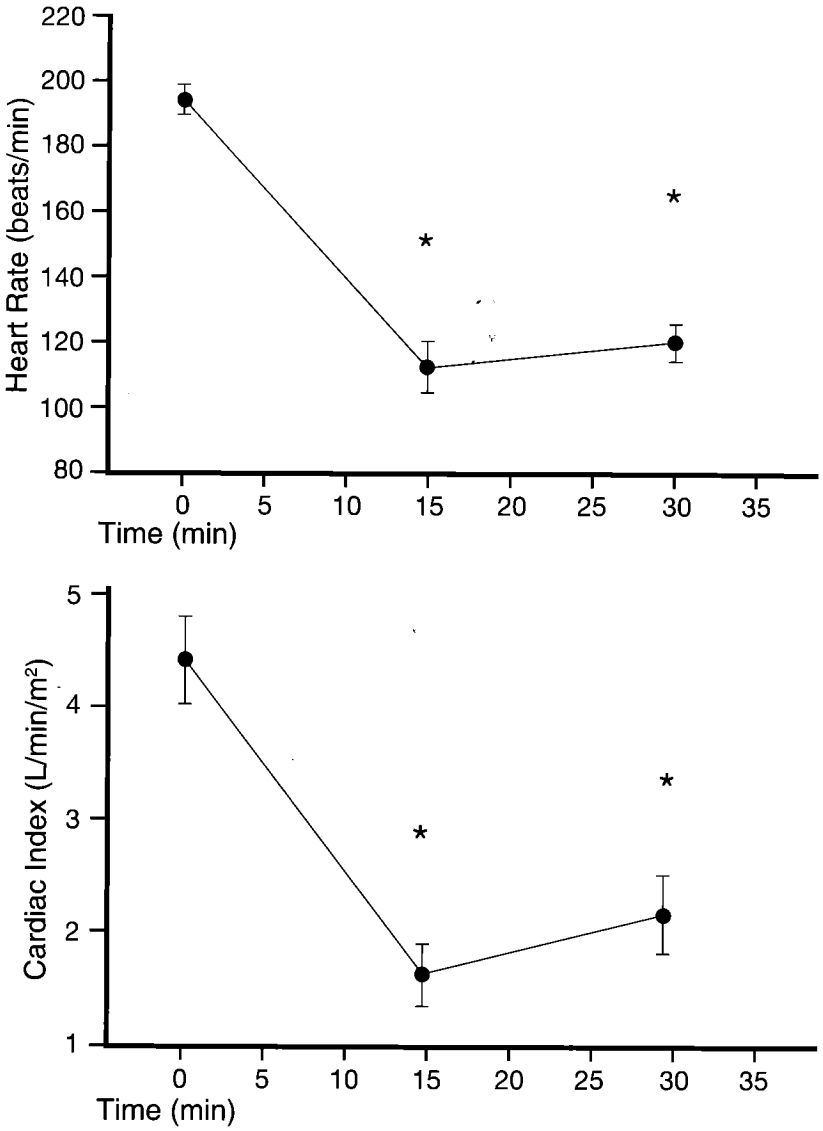


Fig. 9.10. Hemodynamic effects of intramuscular administration of medetomidine (20 μg/kg) in conscious cats. With permission from Lamont et al.[187]

ceptors increases myometrial contractility, and activation of α_2 receptors has limited effects on uterine tone in most species. In dogs, IV administration of medetomidine at a dose of 20 μg/kg decreases electrical activity of the myometrium, and a dose of 40 μg/kg increases electrical activity in dogs during the last trimester of pregnancy.[219] Medetomidine administration also produces significant cardiovascular effects, and use of the drug in animals during the last trimester of pregnancy should be avoided.

Medetomidine administration has dramatic effects on endocrine function in animals. In dogs, IM administration of medetomidine (10 to 80 μg/kg) decreases plasma norepinephrine, epinephrine, and nonesterified fatty acid concentrations for up to 4 h, whereas cortisol and glucagon concentrations do not change.[76] Preoperative administration of α_2-agonists also attenuates the stress response associated with surgical trauma. In dogs undergoing ovariohysterectomy, preoperative administration of medetomidine reduces catecholamine and cortisol concentrations postoperatively.[220,221] Similarly, preoperative administration of medetomidine (20 μg/kg IM) attenuates perioperative increases in norepinephrine, epinephrine, and cortisol concentrations to a greater degree than does acepromazine (Fig. 9.12).[205] Administration of xylazine or medetomidine activates α_2 receptors on pancreatic beta cells and inhibits release of insulin for approximately 2 h.[76,168,222] Although both drugs produce a comparable inhibition of insulin release, medetomidine produces a less dramatic change in plasma glucose concentrations.[76,222] This difference may be due to a difference in selectivity for the α_2 receptor compared with the α_1 receptor. Xylazine, a less selective agonist, appears to increase plasma glucose concentrations directly by activating α_1 receptors and stimulating hepatic glucose production. Changes in catecholamine, nonesterified fatty acids, insulin, and glucose concentrations induced by administration of α_2-agonists (xylazine or medetomidine) are reversed by administration of α_2-antagonists (yohimbine or atipamezole).[223]

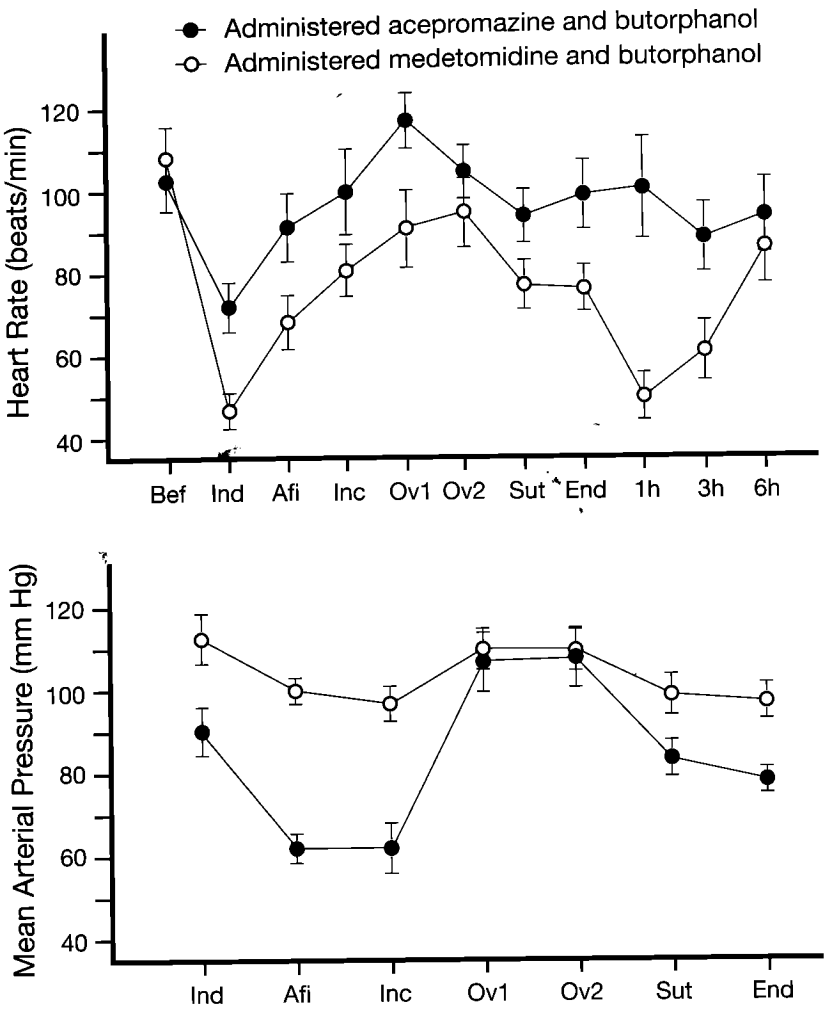


Fig. 9.11. Effects of preoperative intramuscular administration of medetomidine (20 μg/kg) or acepromazine (0.05 mg/kg) on heart rate and mean arterial pressure in dogs anesthetized with isoflurane for ovariohysterectomy. Bef, before surgery; Ind, induction; Afi, after induction; Inc, abdominal incision; OV1, removal of ovary; OV2, removal of second ovary; Sut, abdominal suturing; End, end of surgery; and 1h, 3h, and 6h mean 1 h, 3 h, and 6 h after surgery. With permission from Vaisanen et al.[205]

Medetomidine administration has significant effects on pupillary diameter and intraocular pressure. Topical administration of medetomidine readily induces mydriasis and decreases intraocular pressure in rabbits and cats.[224,225] In contrast, the IV administration of medetomidine to dogs reportedly induces miosis and does not alter intraocular pressure.[226] Administration of medetomidine to dogs and cats can cause vomiting, which increases intraocular pressure dramatically.

Medetomidine administration also has significant effects on cerebral blood flow, intracranial pressure, and thermoregulation. In one study performed in spontaneously breathing dogs anesthetized with isoflurane (0.5 and 1.5 MAC), the administration of dexmedetomidine (10 μg/kg IV) decreased cerebral blood flow but did not alter cerebral metabolic rate.[227] In another study in mechanically ventilated dogs anesthetized with isoflurane (1.0 MAC), the administration of medetomidine (30 μg/kg IV) increased cerebral perfusion pressure but did not change intracranial pressure.[90] Again, administration of medetomidine to dogs and cats can cause vomiting, which increases intracranial pressure dramatically. Decreases in body temperature are attributed to depression of the thermoregulatory center, muscle relaxation, and reduced shivering. In conscious dogs, only slight reductions in body temperature (1°C over 1 h) are observed after IV administration of medetomidine at doses ranging from 1 to 20 μg/kg.[202]

Clinical Uses As an adjunct to general anesthetics, medetomidine has a favorable pharmacodynamic profile in dogs and cats. In addition to providing sedation, analgesia, and muscle relaxation, the preoperative administration of medetomidine substantially reduces the amount of injectable and inhalational anesthetic required to induce and maintain anesthesia. Medetomidine administration also attenuates the stress response to surgical trauma by reducing catecholamine and cortisol levels postoperatively.[220,221] The initial increase in vascular resistance and blood pressure and subsequent bradycardia are potential problems, but these side effects are well tolerated by healthy dogs and cats. Vomiting is also a potential problem for some patients. As a general rule, medetomidine should not be administered to pediatric or geriatric animals, or to animals with significant neurological, cardiovascular, respiratory, hepatic, or renal disease. Once preanesthetic and anesthetic drugs are administered, patients should be monitored carefully throughout the perioperative period, with special attention being paid to heart rate and rhythm.

α_2-Agonists and acepromazine are the only reliable sedatives

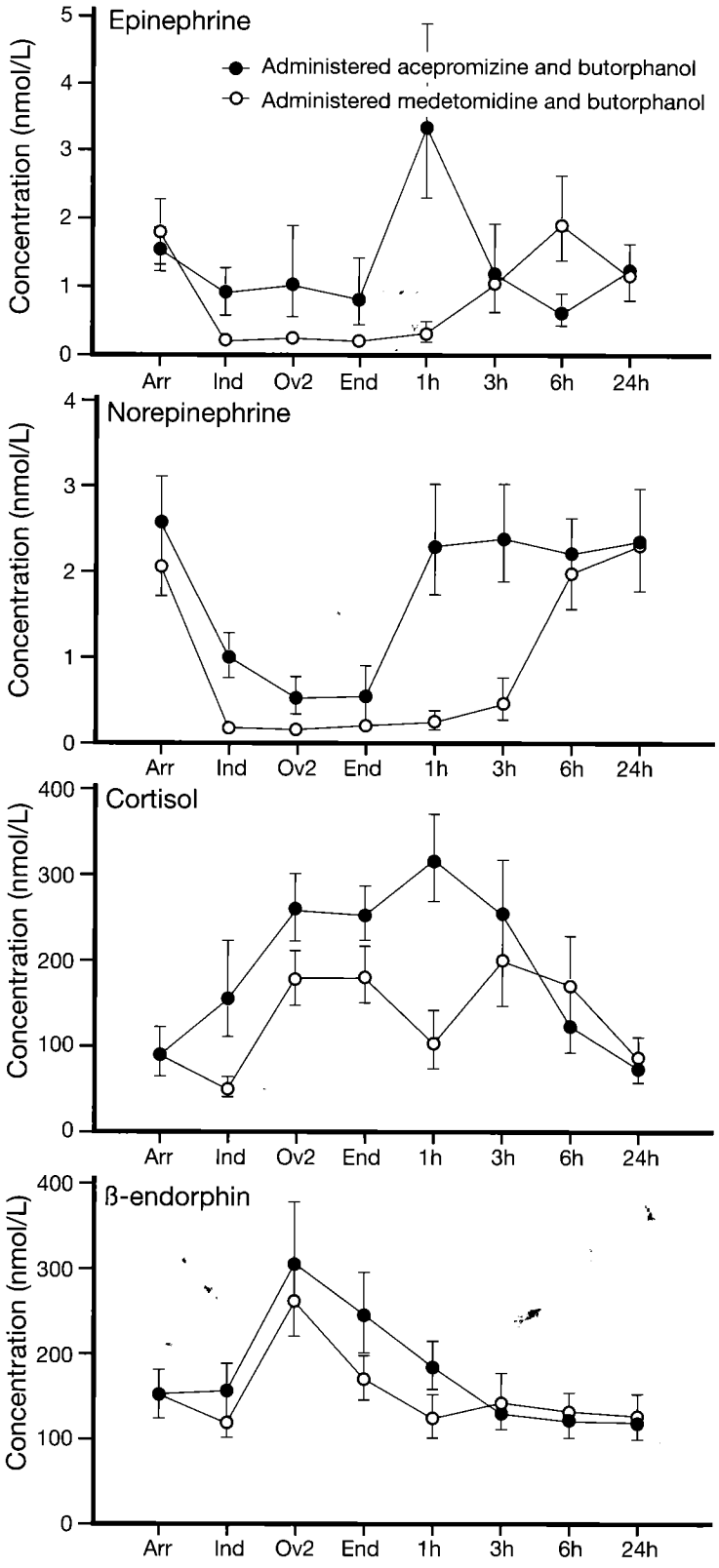


Fig. 9.12. Effects of preoperative intramuscular administration of medetomidine (20 µg/kg) or acepromazine (0.05 mg/kg) on norepinephrine, epinephrine, cortisol, and ß-endorphin concentrations in dogs undergoing ovariohysterectomy. Arr, arrival; Ind, induction; OV2, removal of second ovary; End, end of surgery; and 1h, 3h, 6h, and 24h mean 1 h, 3 h, 6 h, and 24 h after surgery. With permission from Vaisanen et al.[205]

currently available for use in dogs and cats. Acepromazine is routinely used preoperatively to provide sedation for catheter placement and induction of anesthesia, and is often given in combination with opioids to provide both sedation and analgesia. However, acepromazine is not suitable for every patient (e.g., brachycephalics, epileptics, and boxers) and can cause significant hypotension in animals anesthetized with isoflurane.[41] Medetomidine can be administered preoperatively at low doses to healthy dogs and cats, alone or in combination with opioids (Table 9.7).[67] Compared with acepromazine, low doses of

Table 9.7. Medetomidine doses for preoperative sedation and analgesia in healthy dogs and cats

Drugs	Canine Doses[a]	Feline Doses[b]
Medetomidine	10–20 μg/kg IM	20–40 μg/kg IM
with or without		
Atropine	0.04 mg/kg IM	0.04 mg/kg IM
Medetomidine	5–10 μg/kg IM	10–20 μg/kg IM
Butorphanol	0.2–0.4 mg/kg IM	0.2–0.4 mg/kg IM
with or without		
Atropine	0.04 mg/kg IM	0.04 mg/kg IM
Medetomidine	5–10 μg/kg IM	10–20 μg/kg IM
Morphine	0.2–0.4 mg/kg IM	0.2–0.4 mg/kg IM
with or without		
Atropine	0.04 mg/kg IM	0.04 mg/kg IM
Medetomidine	5–10 μg/kg IM	10–20 μg/kg IM
Hydromorphone	0.04–0.08 mg/kg IM	0.04–0.08 mg/kg IM
with or without		
Atropine	0.05 mg/kg IM	0.04 mg/kg IM
Medetomidine	5–10 μg/kg IM	10–20 μg/kg IM
Oxymorphone	0.04–0.08 mg/kg IM	0.04–0.08 mg/kg IM

IM, intramuscularly.
[a]Medetomidine should not be given to dogs with significant neurological, cardiac, respiratory, hepatic, or renal disease. Some of these drugs are not approved for use in dogs in Canada or the United States.
[b]Medetomidine should not be given to cats with significant neurological, cardiac, respiratory, hepatic, or renal disease. Some of these drugs are not approved for use in cats in Canada or the United States.

Table 9.8. Medetomidine and opioid doses for postoperative sedation and analgesia in healthy dogs and cats

Drugs	Canine Doses[a]	Feline Doses[b]
Medetomidine	2–4 μg/kg IM	4–8 μg/kg IM
Medetomidine	1–2 μg/kg IM	2–4 μg/kg IM
Butorphanol	0.1–0.2 mg/kg IM	0.1–0.2 mg/kg IM
Medetomidine	1–2 μg/kg IM	2–4 μg/kg IM
Morphine	0.1–0.2 mg/kg IM	0.1–0.2 mg/kg IM
Medetomidine	1–2 μg/kg IM	2–4 μg/kg IM
Hydromorphone	0.02–0.04 mg/kg IM	0.02–0.04 mg/kg IM
Medetomidine	1–2 μg/kg IM	2–4 μg/kg IM
Oxymorphone	0.02–0.04 mg/kg IM	0.02–0.04 mg/kg IM

IM, intramuscularly.
[a]Medetomidine should not be given to dogs with significant neurological, cardiac, respiratory, hepatic, or renal disease. Some of these drugs are not approved for use in dogs in Canada or the United States.
[b]Medetomidine should not be given to cats with significant neurological, cardiac, respiratory, hepatic, or renal disease. Some of these drugs are not approved for use in cats in Canada or the United States.

medetomidine produce better analgesia for catheter placement and greater reductions in anesthetic requirements, and are less likely to cause hypotension in animals anesthetized with isoflurane. In patients with good cardiopulmonary reserve, the concurrent administration of an anticholinergic agent will prevent bradyarrhythmias while slightly improving cardiac output at the expense of a rather large increase in myocardial work and oxygen consumption. Thus, the use of an anticholinergic preoperatively with α_2-agonists to prevent bradycardia and AV blockade continues to be somewhat controversial.[208,211,228,229] The use of an anticholinergic has been recommended for the following reasons: Firstly, even at low preanesthetic doses, significant bradycardia can occur if an anticholinergic is not administered concurrently. Secondly, the potential for severe vagotonic responses and profound bradycardia, secondary to surgical manipulation and administration of other anesthetic drugs (opioids), is higher during the perioperative period. Thirdly, while the concurrent administration of anticholinergics with high doses of medetomidine can cause dramatic increases in vascular resistance and myocardial work, these increases can be minimized and are generally well tolerated by healthy patients given low doses of medetomidine prior to inhalant (vasodilatory) anesthesia.

Bradycardia and AV blockade are more consistently prevented when anticholinergics are given 10 to 20 min before medetomidine administration, although this is not always practical.[97,211,230] Atropine has a more rapid onset of action than does glycopyrrolate and can be given at the same time as low doses of medetomidine (5 to 20 μg/kg). However, anticholinergic administration increases vagal tone transiently, which can increase the incidence of bradyarrhythmias induced by administration of any α_2-agonist. For example, if atropine or glycopyrrolate is administered at the same time as, or after, high doses of medetomidine (30 to 60 μg/kg), bradycardia and AV blockade are not consistently prevented and ventricular arrhythmias may develop.[228] Therefore, when high doses of medetomidine are administered, the use of anticholinergics should be avoided, heart rate and rhythm should be monitored closely, and atipamezole should be administered to correct severe bradyarrhythmias. Concurrent administration of anticholinergics with α_2-agonist–ketamine combinations should also be avoided, because a prolonged high heart rate can occur.[231]

Very low doses of medetomidine have been given postoperatively to dogs and cats, alone or in combination with opioids (Table 9.8).[67] Administration of selective α_2-agonists in very low doses may enhance and prolong the analgesic effects of opioids, with limited effects on cardiovascular function. Lower doses of opioids may also be used, which reduces the frequency of postoperative respiratory depression. α_2-Agonists also can be used to manage anxiety and dysphoria postoperatively. Because the duration of action of medetomidine is significantly less than that of acepromazine, sedation can be more readily controlled.

Detomidine

This agent is used primarily for sedation and analgesia in horses. The chemical name for the drug is 1H-imidazole, 4-([2,3-

dimethylphenyl]methyl)-hydrochloride (Fig. 9.6). Detomidine is more potent than xylazine and is dosed on a microgram-per-kilogram basis rather than a milligram-per-kilogram basis. The drug produces sedation, analgesia, and muscle relaxation that are comparable to those produced by xylazine in intensity but last longer. In North America and Europe, the drug is sold as detomidine hydrochloride and is approved for use in horses as a sedative-analgesic.

Pharmacokinetics Pharmacokinetic parameters have been determined in calves and horses after IV administration of detomidine at a dose of 50 μg/kg.[232] In calves, the drug is 86% protein bound, and the elimination half-life, clearance, and volume of distribution are 20.0 h, 24.9 mL/min · kg, and 29.4 L/kg, respectively. In horses, the drug is 84% protein bound, and the elimination half-life, clearance, and volume of distribution are 9.7 h, 8.1 mL/min · kg, and 6.8 L/kg, respectively. In calves, detomidine is eliminated primarily by metabolism, and most of the metabolites are excreted in the urine. Tissue liver residues are less than 1 μg/kg at 80 h.

Pharmacodynamics Onset of sedation, analgesia, and muscle relaxation is rapid after IV or IM administration of detomidine. When detomidine is administered IV to horses at a dose of 20 μg/kg, peak sedation and analgesia are achieved within 15 min and persist for approximately 1 h.[116,233] When the same dose is administered IM, depth of sedation and intensity of analgesia are reduced, and peak effects are achieved within 30 min and persist for approximately 1 h.[233] Sedative and analgesic effects are comparable in duration when electrical stimulation is used to evaluate somatic analgesia. Administration of detomidine at a dose of 20 μg/kg induces sedation and analgesia comparable in intensity to, but longer than, those induced by administration of xylazine at a dose of 1.1 mg/kg.[116,233] At these doses, detomidine and xylazine also induce comparable levels of muscle relaxation and ataxia.[116] In a colic model (ponies with cecal balloons), IV administration of detomidine at a dose of 20 μg/kg provides analgesia for 45 min, whereas IV administration of xylazine at a dose of 1.1 mg/kg provides analgesia for approximately 20 min.[234] Sedation lasted longer than analgesia when a cecal balloon was used to evaluate visceral analgesia. In a 2003 placebo-controlled study using electrical stimulation to evaluate somatic analgesia, IV administration of detomidine at a dose of 20 μg/kg provided analgesia for approximately 30 min, whereas administration of xylazine at a dose of 1.1 mg/kg provided analgesia for approximately 15 min (Fig. 9.13).[82] Detomidine administration also reduces catecholamine and cortisol concentrations in horses.[235]

Detomidine administration produces dose-dependent changes in cardiovascular function. In conscious ponies, arterial pressure increases and heart rate decreases by over 50% immediately (1 min) after IV administration of detomidine at doses ranging from 10 to 60 μg/kg.[236] In conscious horses, heart rate decreases by 30% to 35% and cardiac output decreases by 40% to 45% after IV administration at doses of 10 to 20 μg/kg.[237] At these doses, 30% of horses develop AV block within 5 min, heart rate

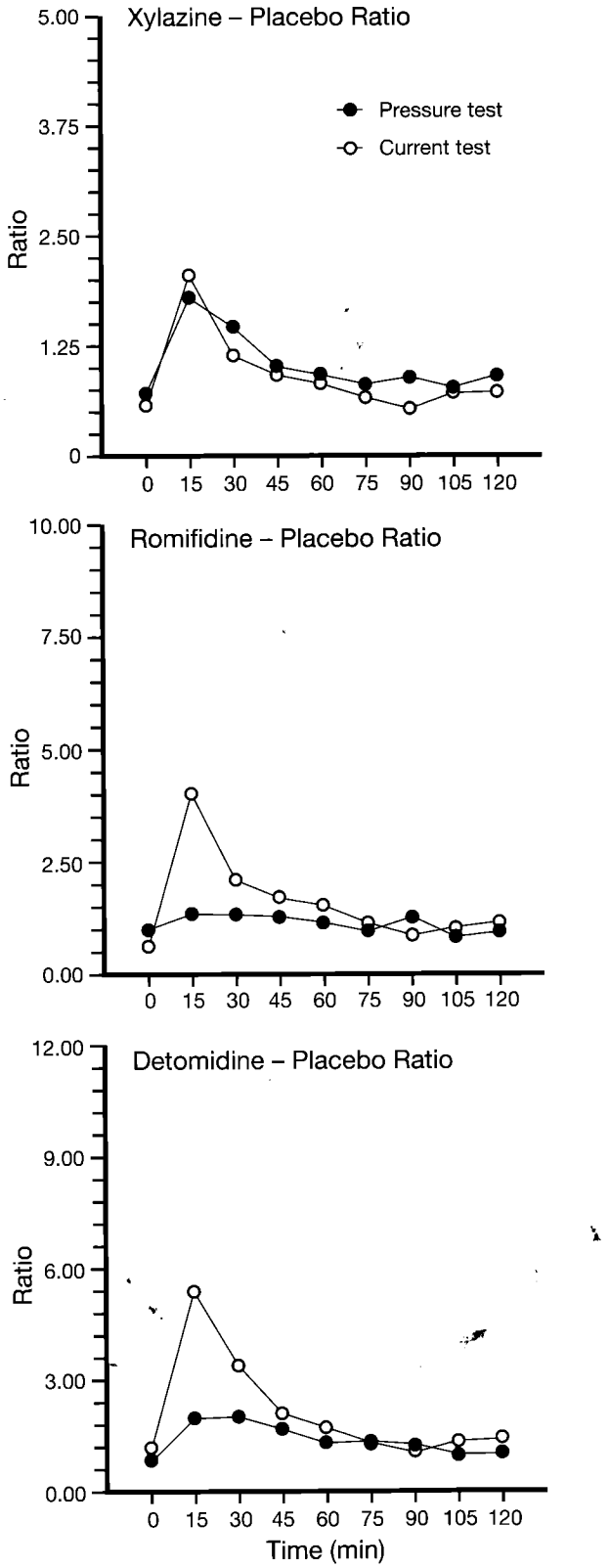


Fig. 9.13. Antinociceptive effects of intravenous administration of xylazine (1.1 mg/kg), detomidine (20 μg/kg), or romifidine (80 μg/kg) in horses. With permission from Moens et al.[82]

and cardiac output are reduced for 45 min to 1 h, and mean arterial pressure is reduced for 90 min to 2 h. After IM administration of detomidine at a dose of 40 μg/kg, heart rate and cardiac output decrease by 27% and 39%, respectively.[237] Intravenous infusion of detomidine at a constant rate produces decreases in heart rate and cardiac output that are comparable to bolus administration, but mean arterial pressure remains elevated for the duration of the infusion.[238] Hematocrit and total protein decrease after parenteral administration of detomidine.[237,238] These changes are probably produced by fluid shifts and sequestration of erythrocytes in the spleen that occur as sympathetic tone decreases.

Detomidine administration has little effect on pulmonary function. Respiratory rate decreases after detomidine administration, but the apparent decrease in minute ventilation appears to coincide with a decrease in carbon dioxide production, and arterial blood-gas values do not change appreciably. In horses administered detomidine IV at doses of 10 to 20 μg/kg, respiratory rate decreases by approximately 50% for 2 h after drug administration.[237] At these doses, arterial pH and PCO_2 do not change, and PO_2 decreases transiently but returns to normal values within 15 to 30 min. The decrease in arterial PO_2 coincides with the dramatic drop in heart rate and cardiac output that occurs immediately after administration of detomidine. Intravenous infusion of detomidine at a constant rate alters respiratory rate and arterial blood-gas values that are comparable to bolus administration.[238]

Detomidine administration has significant effects on esophageal transit time and gastrointestinal motility. In horses, IV administration of detomidine (10 to 20 μg/kg) produces dose-dependent increases in esophageal transit time and retrograde peristalsis, and a decrease in duodenal motility.[239,240] Detomidine administration also reduces cecal and colonic motility in ponies.[153] Detomidine is a very effective visceral analgesic, and its use in horses with colic should not be abandoned because of unwarranted concerns about gastrointestinal side effects. After all, increases in sympathetic tone associated with uncontrolled abdominal pain also reduce gastrointestinal motility.

Detomidine produces sedation and analgesia in horses when administered epidurally at the first intercoccygeal space. Its administration at doses of 30 to 60 μg/kg diluted in 10 mL of sterile water produces perineal analgesia with variable bilateral analgesia up to the 14th thoracic dermatome.[241,242] Analgesia begins in 10 to 15 min and lasts for 2 to 3 h. Doses under 30 μg/kg do not produce reliable analgesia, and those over 60 μg/kg may cause recumbency. The drug is lipophilic and is rapidly absorbed into the systemic circulation from the epidural space. Systemic effects include marked sedation and ataxia, a decrease in heart rate and 2° AV blockade, an increase followed by a decrease in mean arterial pressure, decreases in respiratory rate and arterial PO_2, and diuresis.[241,242] Caudal epidural administration of xylazine (0.25 mg/kg) produces longer-lasting perineal analgesia with fewer systemic side effects than does caudal epidural administration of detomidine.[243] Detomidine has also been administered epidurally in combination with morphine to horses with experimentally induced hind-limb lameness and to horses undergoing bilateral stifle arthroscopy.[244–246]

Clinical Uses Detomidine administration produces reliable sedation, analgesia, and muscle relaxation in horses. The drug is used alone and in combination with butorphanol to produce standing sedation for diagnostic and surgical procedures, and as an analgesic for horses with abdominal pain. Detomidine is usually given IV at doses ranging from 5 to 20 μg/kg, but it can be given IM at doses ranging from 10 to 40 μg/kg. Sedation is more reliable and horses are less responsive to external stimuli when detomidine is given with butorphanol or another opioid.[247] As with other α_2-agonists, excited or fractious animals may require higher doses of detomidine. Ataxia can be a problem in healthy horses, and the drug should be used with discretion in animals with neurological disease. Detomidine administration also produces marked cardiovascular side effects, and it should be used with caution in horses with significant cardiovascular disease and in those with endotoxic or traumatic shock.

Romifidine

This selective α_2-agonist derived from clonidine is used primarily to produce sedation and analgesia in horses. The chemical name for the drug is 2-([2-bromo-6-flourophenyl]imino)-imidazolidine hydrochloride. Romifidine administration produces sedation and analgesia that are comparable in duration to those produced by detomidine administration.[82,116] Muscle relaxation is comparable but with less ataxia than seen with equivalent sedative doses of xylazine or detomidine.[116] Romifidine is approved or licensed for use in horses in North America and Europe. Although not approved for use in small animals, the sedative and cardiovascular effects of romifidine have been reported in both dogs and cats.[248–251]

Pharmacokinetics and Pharmacodynamics Onset of sedation and analgesia is rapid after parenteral administration of romifidine. When romifidine is administered IV to horses at doses of 40 to 80 μg/kg, sedation begins within 2 min, peak effects are reached within 10 min, and sedation lasts for 40 to 80 min.[116] Similar results were reported after IV administration of romifidine at a dose of 80 μg/kg (Fig. 9.13).[82] In small animals, romifidine has a longer duration of action than xylazine or medetomidine. In dogs, the IM administration of romifidine at doses of 10 to 40 μg/kg produces mild to moderate sedation within 10 min and lasts for 1 to 2 h.[248] Sedation produced by IM administration of romifidine at a dose of 40 μg/kg is comparable in intensity to that produced by xylazine at a dose of 1 mg/kg but lasts longer.[248] The onset of action is faster after IV administration of romifidine at doses ranging from 20 to 120 μg/kg, but the incidence of neuromuscular, respiratory, and cardiovascular side effects increases.[249,250] In cats, IM administration of romifidine (40 μg/kg) in combination with butorphanol produces moderate sedation.[251]

Romifidine can also be used preoperatively to facilitate induction of anesthesia with ketamine and postoperatively to facilitate recovery from inhalational anesthesia. In horses, administration of romifidine before induction of anesthesia with diazepam and ketamine produces short-term anesthesia that is comparable to that produced by preanesthetic administration of xylazine.[252] Romifidine has also been used as a preanesthetic before induc-

tion and maintenance of anesthesia with ketamine and halothane, respectively.[253] Small doses of romifidine have also been administered postoperatively to facilitate recovery from isoflurane anesthesia.[254] Like other α_2-agonists, preanesthetic administration of romifidine (20 to 40 μg/kg IV) to dogs reduces the amount of thiopental or propofol required to induce anesthesia by 40% to 60% and the amount of halothane required to maintain anesthesia by 20%.[255,256]

At doses that produce equivalent degrees of sedation, romifidine produces changes in cardiovascular function that are comparable to those produced by other α_2-agonists. In conscious horses, IV administration of romifidine (80 μg/kg) induces a 20% increase in mean arterial pressure and a 30% to 60% decrease in heart rate within 5 min.[257] During the next 30 min, bradycardia persists, AV blockade is common, and cardiac output decreases by 30% to 40%.[257,258] As with other α_2-agonists, respiratory rate decreases, but arterial pH, PCO_2, and PO_2 do not change, and gastrointestinal motility decreases after romifidine administration.[257–259] In dogs, IV administration of romifidine at doses ranging from 5 to 50 μg/kg induces a dose-dependent increase in mean arterial pressure and decreases in heart rate and cardiac output.[260] After IM administration of romifidine (20 to 40 μg/kg), bradycardia lasts for up to 2 h, respiratory rate decreases, and arterial pH, PCO_2, and PO_2 do not change.[18] Administration of glycopyrrolate 15 min before administration of romifidine (20 to 40 μg/kg IM) reduces the incidence and severity of bradycardia but is associated with a dose-dependent increase in mean arterial pressure.[18]

Clinical Uses Romifidine administration produces reliable sedation and analgesia in horses. The drug is used alone and in combination with butorphanol to produce standing sedation for diagnostic and surgical procedures, and can also be used as an analgesic. Romifidine is usually administered IV to horses at doses ranging from 40 to 80 μg/kg and produces less ataxia than equivalent sedative doses of xylazine or detomidine.[116] Sedation is more reliable and horses are less responsive to external stimuli when romifidine is administered in combination with butorphanol.[257,261] Romifidine (100 μg/kg IV) has also been given as a preanesthetic before induction of anesthesia with diazepam and ketamine.[252] As with other α_2-agonists, fractious or excited animals may require higher doses of romifidine. Romifidine also produces marked cardiovascular side effects and should be used with caution in horses with significant cardiovascular disease and in those with endotoxic or traumatic shock. Romifidine is not labeled for use in dogs and cats, and its use in small animals is not recommended until further studies are completed.

α_2-Antagonists

α_2-Antagonists are used to reverse the sedative and cardiovascular effects of α_2-agonists. Currently, three antagonists (tolazoline, yohimbine, and atipamezole) are available for use in animals. Tolazoline is a relatively nonselective α-receptor antagonist, and receptor binding or selectivity ratios (α_2/α_1) for yohimbine and atipamezole are 40:1 and 8526:1, respectively.[262] Tolazoline and yohimbine are used primarily to reverse the effects of xylazine in dogs, cats, ruminants, and several exotic species.[63,263] Atipamezole is used primarily to reverse the effects of medetomidine is dogs, cats, and several exotic species.[69,264–266]

In addition to reversing the sedative and cardiovascular effects of α_2-agonists, α_2-antagonists can produce significant side effects. If a relative overdose of an antagonist is administered, neurological (excitement and muscle tremors), cardiovascular (hypotension and tachycardia), and gastrointestinal (salivation and diarrhea) side effects can occur. Death has also been reported after rapid IV administration of tolazoline or yohimbine to sheep sedated with xylazine.[267] Therefore, the dose of antagonist should be calculated carefully, and these calculations should be based on the amount of agonist administered initially and the time that has elapsed since the agonist was administered. Generally, calculations are based on an agonist/antagonist ratio, not a simple milligram-per-kilogram calculation. When in doubt, it is usually better to underdose than to overdose the antagonist. α_2-Mediated analgesia is also reversed, and antagonists should be used with discretion postoperatively.

Tolazoline

This agent is a nonselective α-receptor antagonist used primarily to reverse the sedative and cardiovascular effects of xylazine in ruminants.[63,263] The drug is a synthetic imidazoline derivative (2-benzyl-2-imidazoline) that produces histaminergic and cholinergic effects in addition to producing nonspecific blockade of α receptors (Fig. 9.14). Tolazoline is approved for use in horses in Canada but not the United States.

Pharmacokinetics and Pharmacodynamics Tolazoline is effective in reversing the sedative cardiovascular and gastrointestinal effects of xylazine in ruminants. Administration of tolazoline (2 mg/kg IV) reverses the sedative and cardiovascular effects of xylazine (0.3 to 0.4 mg/kg IV) in sheep, 5- to 7-month old calves, and adult cattle equally well.[142,267–270] In steers and lactating dairy cattle given tolazoline IV at a relatively high dose (4 mg/kg), tolazoline concentrations were below 10 μg/kg by 4 days in tissue samples and by 2 days in milk samples.[113]

Clinical Uses Tolazoline is used primarily to reverse the sedative and cardiovascular effects of xylazine in ruminants. Dose calculations are made based on an agonist/antagonist ratio of approximately 1:10. Therefore, if the initial xylazine dose is 0.1 to 0.2 mg/kg, then tolazoline would be administered IV at a dose of 1 to 2 mg/kg. The time that has elapsed since the agonist was administered should be considered, as well. Tolazoline should be administered slowly when given IV to avoid neurological (excitement) and cardiovascular (hypotension and tachycardia) side effects.

Yohimbine

This agent is used as a selective α_2-receptor antagonist of the sedative and cardiovascular effects of xylazine in dogs, cats, and several exotic species.[63,263] This drug is an indolealkylamine alkaloid (17-hydroxyyohimban-16-carboxylic acid methyl ester) that is related structurally to reserpine (Fig. 9.14). At high con-

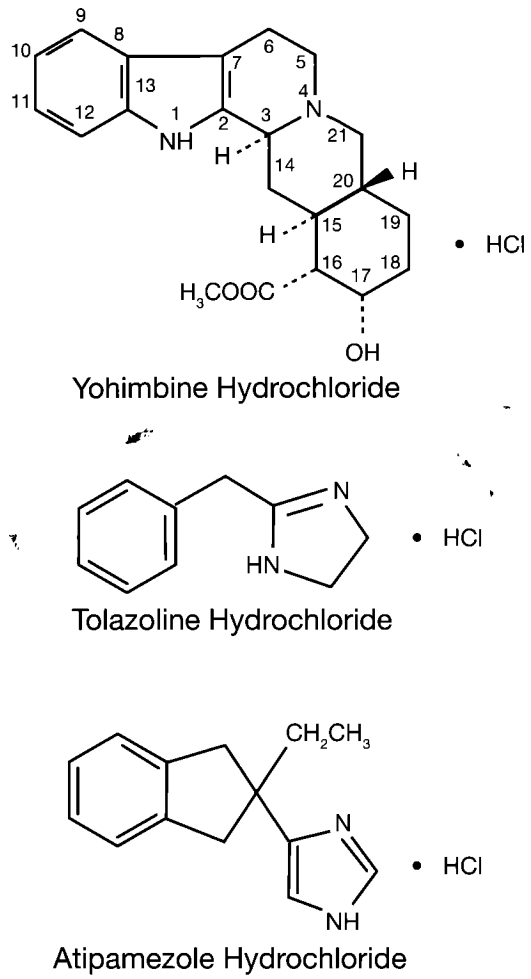


Fig. 9.14. Chemical structures of α_2-receptor antagonists. With permission from Gross.[325]

centrations, yohimbine may interact with dopaminergic and serotonergic receptors, and, at very high concentrations, it may have a nonspecific local anesthetic effect.[271] Yohimbine is approved for use in dogs in Canada and in dogs and deer in the United States.

Pharmacokinetics and Pharmacodynamics The pharmacokinetics of yohimbine have been reported for dogs, horses, and cattle.[272]

In dogs given yohimbine (0.4 mg/kg IV), the volume of distribution, total body clearance, and elimination half-life were 4.5 L/kg, 30 mL/min · kg, and 104 min, respectively. In horses given yohimbine (0.15 mg/kg IV), the volume of distribution, total body clearance, and elimination half-life were 4.6 L/kg, 40 mL/min · kg, and 76 min, respectively. In cattle given yohimbine (0.25 mg/kg IV), the volume of distribution, total body clearance, and elimination half-life were 4.9 L/kg, 70 mL/min · kg, and 47 min, respectively.

Many reports on a variety of species have documented yohimbine's efficacy in antagonizing the various actions of xylazine. Examples include use in dogs where yohimbine (0.1 mg/kg IV) reverses the sedative and cardiovascular effects of xylazine (1 mg/kg) when administered IV or IM[263,273–275] and in cats where yohimbine (0.5 mg/kg IV) reverses the sedative and cardiovascular effects of xylazine (1 mg/kg IM).[263] In white-tailed deer, yohimbine (0.3 mg/kg IV) reportedly reverses the sedative and cardiovascular effects of a high dose of xylazine (3 mg/kg IM),[263,276] whereas, in calves, it (0.25 mg/kg IV) rapidly reverses the cardiovascular and gastrointestinal effects of xylazine (0.05 mg/kg IV), with minimum effect on sedation.[277]

Clinical Uses Dose calculations are made based on agonist/antagonist ratios of approximately 10:1, 2:1, and 10:1, for dogs, cats, and deer, respectively. Therefore, if the initial dose of xylazine is 0.5 mg/kg for a dog, then yohimbine would be given IV at a dose of 0.05 mg/kg. The time that has elapsed since the agonist was administered should be considered, as well. Like tolazoline, yohimbine is usually administered slowly IV to avoid neurological (excitement) and cardiovascular (hypotension and tachycardia) side effects.

Atipamezole

This highly selective α_2-receptor antagonist is used to reverse the sedative and cardiovascular effects of medetomidine in dogs, cats, and several other species.[69,264–266,278] The chemical name of the drug is (4-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (Fig. 9.14). Atipamezole is 200 to 300 times more selective for the α_2 receptor than is yohimbine and has no effect at β-adrenergic, dopaminergic, serotonergic, histaminergic, muscarinic, opiate, γ-aminobutyric acid (GABA), or benzodiazepine receptors.[262] Atipamezole is approved for use in dogs in North America and Europe.

Pharmacokinetics and Pharmacodynamics The pharmacokinetics of atipamezole (250 μg/kg IM), alone and 30 min after administration of medetomidine (50 μg/kg IV), have been reported for dogs.[279] When atipamezole is given alone, peak plasma concentrations are reached within 15 min, and the volume of distribution, total body clearance, and elimination half-life are 2.3 L/kg, 27 mL/min · kg, and 56 min, respectively. When atipamezole is given after medetomidine, peak plasma concentrations are reached within 25 min, and the volume of distribution, total body clearance, and elimination half-life are 2.5 L/kg, 24 mL/min · kg, and 72 min, respectively. Apparently, prior administration of medetomidine reduces cardiac output and hepatic blood flow, which delays absorption and metabolism of atipamezole.

Atipamezole is used primarily to reverse the sedative and cardiovascular effects of medetomidine in dogs.[264,265] Animals given atipamezole (200 μg/kg IM), 15 to 30 min after administration of medetomidine (40 μg/kg IM), show increases in heart rate and initial signs of arousal within 5 min and are walking within 10 min. Occasionally, tachycardia and excitation occur shortly after atipamezole administration, and resedation can occur 30 to 60 min after administration of the antagonist. Atipamezole has also been used to reverse the sedative and cardiovascular effects of medetomidine in cats.[266] Cats administered atipamezole (200 to 400 μg/kg IM), 15 to 30 min after administration of medetomidine (100 μg/kg IM), show increases in heart rate and initial signs of arousal within 5 min and are walking within 10 min. Occasionally,

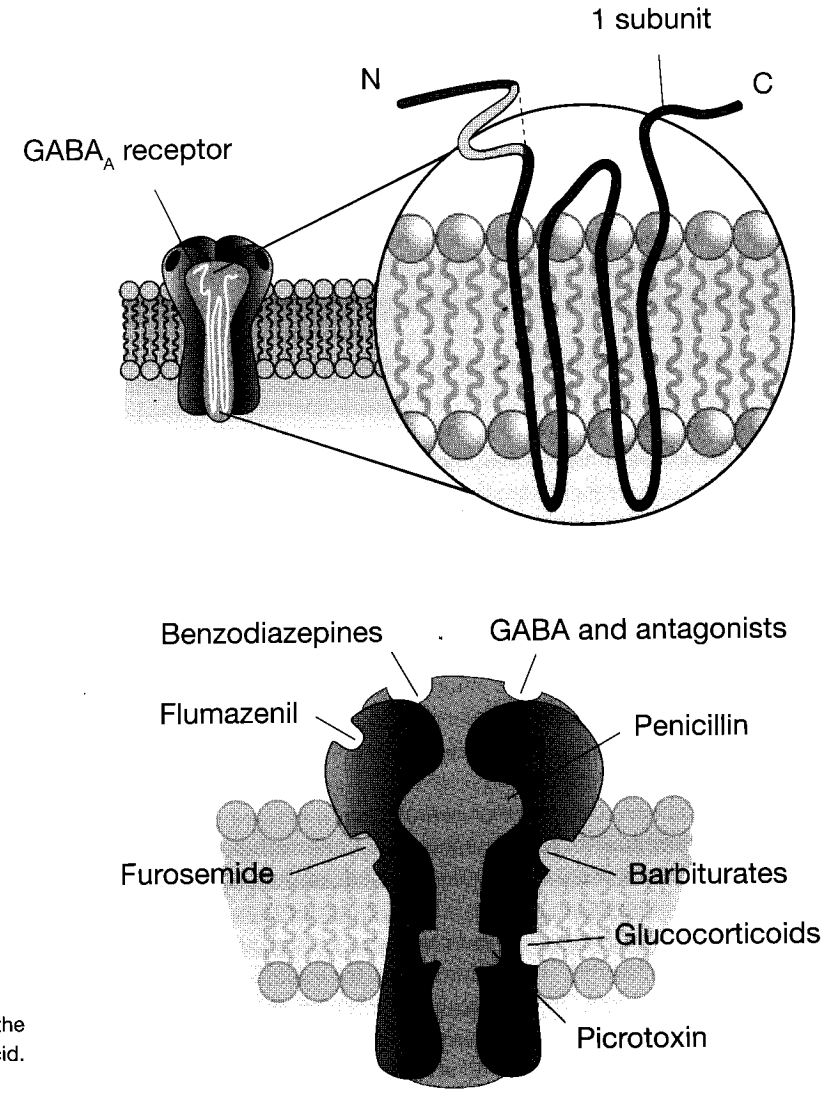


Fig. 9.15. The structure and major binding sites of the GABA$_A$-receptor complex. GABA, γ-aminobutyric acid. With permission from Chou.[326]

tachycardia and excitation occur shortly after atipamezole administration. Atipamezole has also been used to reverse the sedative effects of medetomidine in cattle[278] and several exotic species.[69] Medetomidine/atipamezole ratios for nondomestic carnivores and ruminants are 1:2–3 and 1:4–5, respectively. Atipamezole has been used to reverse the sedative and cardiovascular effects of xylazine in several species.[69,280–283] The xylazine/atipamezole ratio for reversal of most mammals is approximately 10:1.

Clinical Uses Atipamezole is usually administered to reverse the effects of medetomidine after nonpainful diagnostic or therapeutic procedures, and it is not usually administered perioperatively. Complete reversal of the sedative, analgesic, and cardiovascular effects of medetomidine is achieved when atipamezole is administered IM to dogs and cats at four to six times and two to four times the dose of medetomidine, respectively.[265,266] Therefore, if the initial dose of medetomidine is 20 μg/kg for a dog, then atipamezole would be given IM at a dose of 100 μg/kg. Similarly, if the initial dose of medetomidine is 40 μg/kg for a cat, then atipamezole would be given IM at a dose of 120 μg/kg. In both of these examples, the dose of atipamezole should be reduced if more than 30 min has elapsed since medetomidine administration. Because of the potential for excitation and cardiovascular side effects (hypotension and tachycardia), atipamezole is not labeled for IV use. However, it can be given IV to reverse the cardiovascular effects of medetomidine in emergency situations. Atipamezole and anticholinergics can both cause dramatic increases in heart rate, and the concurrent use of these drugs should be avoided.

Benzodiazepine Agonists

Benzodiazepines produce most of their pharmacological effects by modulating GABA-mediated neurotransmission.[284] GABA is the primary inhibitory neurotransmitter in the mammalian nervous system and cell membranes of most CNS neurons express GABA receptors. These receptors are also found outside the CNS in autonomic ganglia. Two main types of GABA receptors are involved in neuronal transmission: The GABA$_A$ receptor complex is a ligand-gated chloride channel that consists of a central pore surrounded by five glycoprotein subunits (Fig. 9.15).

Activation requires binding of GABA molecules to both α subunits of the receptor. The $GABA_B$ receptor is a metabotropic receptor that consists of a single glycoprotein subunit that is closely associated with a G protein. These G proteins are coupled directly to potassium or calcium channels or to a second-messenger system (adenylate cyclase or phospholipase C). Activation of ionotropic $GABA_A$ receptors increases chloride conductance rapidly and generates fast inhibitory postsynaptic potentials. Activation of metabotropic $GABA_B$ increases potassium conductance slowly and generates slow inhibitory postsynaptic potentials. Presynaptic $GABA_B$ autoreceptors are coupled to calcium channels and regulate neurotransmitter release.

The benzodiazepine-binding site, as well as the binding sites for other injectable anesthetics (barbiturates, propofol, and etomidate), is located on the $GABA_A$ receptor complex (Fig. 9.15). Benzodiazepines enhance binding between GABA and the $GABA_A$ receptor, and increase the frequency of channel opening. In contrast, barbiturates enhance intrinsic activity and increase the duration of channel opening. Both mechanisms increase chloride conductance and hyperpolarize the cell membrane, which reduces neuronal excitability. Benzodiazepines have no intrinsic agonist activity and cannot alter chloride conductance in the absence of GABA. This lack of intrinsic activity limits CNS depression and provides benzodiazepines with a much wider margin of safety than barbiturates.

Modulation of GABA-mediated neurotransmission also plays a role in nociception.[285] At the supraspinal level, activation of $GABA_A$ receptors inhibits descending antinociceptive pathways and enhances sensitivity to noxious stimuli. In fact, systemic administration of benzodiazepines and barbiturates antagonizes the analgesic effect of opioids.[286,287] However, at the spinal level, activation of $GABA_A$ and $GABA_B$ receptors produces an antinociceptive effect, and antagonism of spinal $GABA_B$ receptors may contribute to the development of allodynia.

Ligands that bind to benzodiazepine receptors are classified as agonists, inverse agonists, and antagonists. *Agonists* bind to benzodiazepine receptors and produce sedative, anxiolytic, muscle relaxant, and anticonvulsant effects in most animals. *Inverse agonists* bind to the same receptor and produce the opposite effects. *Antagonists* have high affinity for the benzodiazepine receptor and have little or no intrinsic activity. These ligands block or reverse the effects of both agonists and inverse agonists. Diazepam, midazolam, and zolazepam are the benzodiazepine agonists used most commonly in animals. Diazepam and midazolam are used primarily as sedatives, muscle relaxants, and anticonvulsants. Zolazepam is available in combination with a dissociative anesthetic (tiletamine), which is approved for use as an anesthetic in dogs and cats in the United States.

Diazepam

This is the most widely used benzodiazepine in both small and large animals. The chemical name for the drug is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Fig. 9.16). Diazepam is not soluble in water, and parenteral formulations contain 40% propylene glycol and 10% ethanol. Because of this insolubility, diazepam should not be mixed with diluents or other drugs. Further, the drug should not be administered IM because it is very irritating and is poorly absorbed. The parenteral formulation of diazepam is administered by slow IV injection to avoid pain, thrombophlebitis, and cardiotoxicity. The drug is also sensitive to light and adheres to plastic, so therefore should not be stored in plastic syringes for extended periods.[288] Diazepam is used primarily as a muscle relaxant and as an anticonvulsant for dogs, cats, and horses. The drug is not approved for use in animals in Canada or the United States.

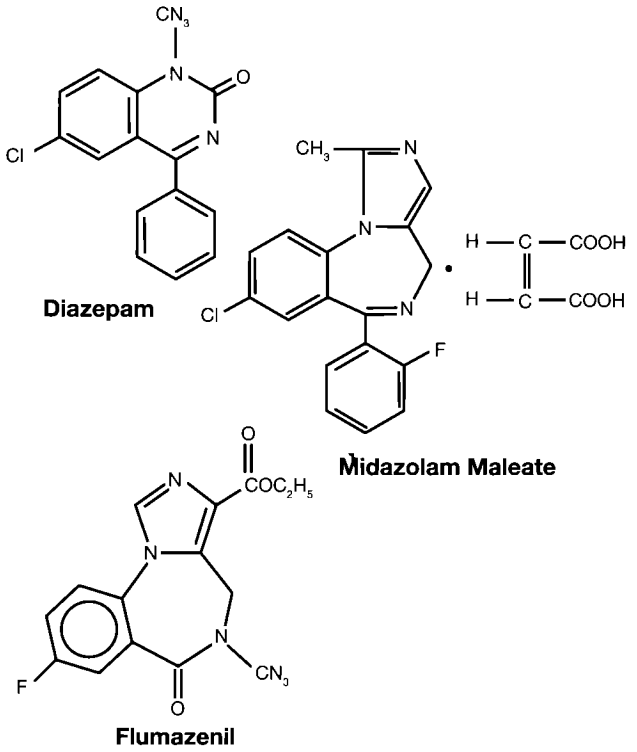


Fig. 9.16. Chemical structures of benzodiazepine receptor agonists and antagonists. With permission from Gross.[325]

Pharmacokinetics Diazepam is highly lipid soluble and is rapidly distributed throughout the body. Approximately 90% of the drug is protein bound, and diazepam is metabolized by demethylation and hydroxylation to *N*-desmethyldiazepam (nordiazepam), 3-hydroxydiazepam, and oxazepam.[289] Nordiazepam and oxazepam produce significant pharmacological effects at clinically relevant concentrations. The pharmacokinetics of diazepam have been determined in dogs, cats, and horses. In dogs, the elimination half-life of diazepam after administration of a relatively high dose (2 mg/kg IV) is 3.2 h.[290] Nordiazepam appears rapidly in plasma and quickly exceeds concentrations of diazepam, whereas oxazepam concentrations peak within 2 h. The elimination half-lives of nordiazepam and oxazepam are 3.6 and 5.7 h, respectively. In cats, the mean elimination half-life of diazepam after administration of relatively high doses (5, 10, and 20 mg/kg IV) is 5.5 h.[291] Approximately 50% of the diazepam

dose is converted to nordiazepam, and the mean elimination half-life of the metabolite is 21 h—which is approximately four times longer than the half-life of diazepam. In horses, the elimination half-life ranges from 7 to 22 h after IV administration of diazepam at a dose 0.2 mg/kg.[292] Metabolites are not detectable in plasma, but glucuronide conjugates are detectable in the urine. In contrast to dogs and cats, conjugation and elimination of the nordiazepam and oxazepam is rapid in the horse.

Pharmacodynamics Diazepam does not sedate dogs and horses reliably, and can cause excitement, dysphoria, and ataxia. In dogs, IV administration of diazepam (0.5 mg/kg) produces arousal and excitement.[293] Diazepam administration can produce dysphoria and aggressive behavior in cats, and the drug should be used with caution in this species.[120] In horses, IV administration of diazepam at doses greater than 0.2 mg/kg produces mild sedation but also marked muscle relaxation, ataxia, and recumbency.[292] Because of these behavioral effects, diazepam alone has limited value as a sedative for dogs, cats, and horses. In dogs and horses, it is used primarily as a muscle relaxant before induction of anesthesia with ketamine. Diazepam administration (0.3 to 0.5 mg/kg IV) immediately before ketamine administration improves muscle relaxation and facilitates intubation in dogs.[293,294] In horses premedicated with xylazine, diazepam administration (0.05 to 0.1 mg/kg IV) immediately before ketamine administration improves muscle relaxation and induction quality.[295] In cats premedicated with diazepam and then administered either ketamine or thiopental, dysphoria and aggressive behavior can occur during the recovery period.[120,296] This type of aberrant behavior limits the utility of diazepam as an anesthetic adjunct in cats.

Diazepam administered preoperatively reduces injectable and inhalational anesthetic requirements. Preoperative administration of diazepam (0.1 to 0.2 mg/kg IV) reduces the dose of thiamylal required to induce anesthesia, whereas the intraoperative administration reduces the amount of inhalant required to maintain anesthesia.[297] Diazepam reduces isoflurane requirements by 20% in dogs anesthetized with isoflurane and fentanyl.[298] Similarly, in horses, diazepam administration (0.04 mg/kg) reduces halothane requirement by 29%.[299] Not surprisingly, diazepam administration (0.2 mg/kg IV) decreases the absolute power of the electroencephalogram in all frequencies in dogs anesthetized with isoflurane.[300]

Diazepam produces limited effects on cardiovascular and pulmonary function in animals. In dogs, heart rate, myocardial contractility, cardiac output, and arterial blood pressure do not change appreciably after the IV administration of diazepam at doses of 0.5, 1.0, and 2.5 mg/kg.[301] The IV administration of diazepam at a dose of 0.5 mg/kg followed by the IV administration of ketamine (10 mg/kg) increases heart rate, as well cardiac output, with little change in blood pressure.[293] Respiratory rate decreases, but tidal volume is unchanged after ketamine administration. In horses, IV administration of diazepam over a wide range of doses (0.05 to 0.4 mg/kg) does not produce significant changes in heart rate, cardiac output, arterial blood pressure, respiratory rate, or arterial blood-gas values.[292]

Clinical Uses Diazepam is not a reliable sedative, but is a good muscle relaxant and anticonvulsant in most species. In dogs, diazepam is commonly administered IV at a dose of 0.3 to 0.5 mg/kg immediately before induction of anesthesia with ketamine.[293,302] Diazepam also can be administered prior to induction of anesthesia with thiopental, propofol, etomidate, or an opioid. Diazepam appears to be a more reliable sedative in older dogs and can be administered alone or in combination with an opioid to produce sedation in this subpopulation. In horses premedicated with xylazine or romifidine, diazepam is routinely administered IV at a dose of 0.05 to 0.1 mg/kg immediately before induction of anesthesia with ketamine.[295,303] Diazepam is also a reliable sedative in foals under 1 month of age and can be administered IV at a dose of 0.1 to 0.2 mg/kg. Higher doses are often administered when diazepam is used as an anticonvulsant. In small animals, diazepam in administered IV at a dose of 0.5 to 1.0 mg/kg to control seizures, and, in large animals, a dose of 0.1 to 0.2 mg/kg is usually effective. Again, the parenteral formulation of diazepam is very irritating and potentially cardiotoxic, and should always be administered by slow IV injection.

Midazolam

This is probably the most underutilized sedative in veterinary medicine. Although the drug is not a reliable sedative in dogs and cats, it produces excellent sedation and muscle relaxation in many small mammals (ferrets and rabbits), some large mammals (swine), and many birds. Midazolam is a benzodiazepine with a fused imidazole ring that accounts for the water solubility of the drug at pH values below 4.0. The chemical name of midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-α)(1,4)-benzodiazepine (Fig. 9.16). The pH of the parenteral formulation is 3.5, and the drug is light sensitive like diazepam. After injection, midazolam changes its chemical configuration and becomes lipid soluble at physiological pH. Unlike diazepam, the drug is nonirritating and well absorbed after IM administration. Midazolam is used primarily as a perioperative sedative and muscle relaxant in ferrets, rabbits, swine, and birds. In dogs, it can be used as a sedative in older or debilitated animals, and in combination with ketamine to induce anesthesia. Midazolam is not approved for use in animals in Canada or the United States.

Pharmacokinetics In dogs, midazolam is almost completely (>90%) absorbed after IM injection, and peak plasma concentrations are reached within 15 min.[304] The drug is also highly protein bound (>95%) and rapidly crosses the blood-brain barrier. Midazolam is hydroxylated in the liver, and glucuronide conjugates are excreted in the urine.[305] After IV administration of midazolam (0.5 mg/kg), the volume of distribution, elimination half-life, and clearance are 3.0 L/kg, 77 min, and 27 mL/kg · min, respectively.[304] In dogs given midazolam (0.5 mg/kg IV) and ketamine (10 mg/kg IV) as a bolus, the elimination half-life of midazolam is 28 min.[306] In dogs anesthetized with enflurane, the volume of distribution, elimination half-life, and clearance of midazolam when given IV as a bolus are 3.9 L/kg, 98 min, and 29 mL/kg · min, respectively.[307] In piglets given midazolam (0.4 mg/kg) IV or intranasally, the elimination half-lives were 138

and 158 min, respectively.[308] Bioavailability is 64% and maximum plasma concentrations are reached within 5 min after intranasal administration.

Pharmacodynamics Midazolam is more lipophilic than diazepam and has twice the affinity for the benzodiazepine receptor. It also appears to have a greater sedative effect than diazepam in most species. Onset of sedation and muscle relaxation is rapid after IV or IM administration in most species. In most dogs administered midazolam (0.5 mg/kg) IV or IM, muscle relaxation, ataxia, transient agitation, or mild sedation are quickly observed.[304] In cats administered midazolam IV or IM over a wide range of doses (0.05 to 5.0 mg/kg), muscle relaxation becomes evident but so does arousal and excitement in many cats.[309–311] Some cats are difficult to approach and restrain after midazolam administration. Likewise, many cats administered midazolam and ketamine exhibit abnormal behavior (excitation or vocalization) during recovery. In contrast to its effect on cats, midazolam reliably sedates many other small mammals. In ferrets and rabbits, IM administration of midazolam at a dose of 0.5 to 1.0 mg/kg produces excellent sedation and muscle relaxation. It can also be administered intranasally to rabbits at dose of 2.0 mg/kg.[312] In piglets and adult swine, midazolam is an effective sedative when administered either IM or intranasally at a dose of 0.1 to 0.2 mg/kg.[308,313] In parrots and raptors, IM administration of midazolam at dose of 0.5 to 1.0 mg/kg produces mild to moderate sedation and muscle relaxation. It is also effective as a sedative in quail and geese when administered IM at doses ranging from 2 to 4 mg/kg.[314,315]

Midazolam is commonly given to enhance muscle relaxation and facilitate intubation in dogs and cats coadministered ketamine.[294,311] Preanesthetic administration (0.1–0.2 mg/kg IV) reduces the induction dose of barbiturates and propofol and the concentration of isoflurane required to maintain anesthesia during surgery.[316–318] Like diazepam, midazolam (0.2 mg/kg IV) decreases the absolute power of the electroencephalogram in dogs anesthetized with isoflurane.[319]

Midazolam administration produces minimal effects on cardiopulmonary function in mammals and birds. In dogs, heart rate and cardiac output increase by 10% to 20% after IV administration of midazolam at doses of 0.25 and 1.0 mg/kg.[301] In swine, even though heart rate decreases by 20% and respiratory rate decreases by 50%, cardiac output and blood-gas values do not change after IM midazolam injection (0.1 mg/kg).[313] The IV coadministration of midazolam with ketamine induces changes in cardiopulmonary function comparable to those induced by diazepam and ketamine in dogs.[294]

Clinical Uses Midazolam can be used alone and in combination with opioids to sedate older dogs, small mammals, swine, and birds. It is also administered in combination with injectable anesthetics to improve muscle relaxation and to reduce the dose of anesthetic required to induce anesthesia. Because midazolam has limited effects on cardiopulmonary function, the drug is an ideal sedative for many older or compromised animals. In dogs, midazolam is typically administered alone at doses of 0.2 to 0.4 mg/kg IM or in combination with opioids (butorphanol, hydromorphone, or oxymorphone) to induce sedative-analgesic effects. It can be administered IV at doses of 0.1 to 0.2 mg/kg before induction of anesthesia with ketamine, thiopental, propofol, or etomidate. In ferrets and rabbits, midazolam is administered IM at doses of 0.5 to 1.0 mg/kg, either alone or in combination with opioids (butorphanol or hydromorphone), prior to induction of anesthesia with ketamine. A 0.5- to 1.0-mg/kg dose given IM alone or in combination with butorphanol before induction of anesthesia with isoflurane or sevoflurane has proven quite effective in calming parrots and raptors. Midazolam is also an excellent sedative for most birds undergoing routine diagnostic procedures. In swine, midazolam is typically given IM at doses of 0.1 to 0.2 mg/kg, alone or in combination with opioids, prior to induction with ketamine. Midazolam can also be combined with ketamine to immobilize swine for diagnostic procedures and to facilitate placement of IV catheters. Anticonvulsant doses of midazolam are comparable to those for diazepam in most species. Midazolam is not approved for use in animals in Canada or the United States.

Benzodiazepine Antagonists

These bind to the $GABA_A$ receptor complex and block the effects of both agonists and inverse agonists. Antagonists have a strong affinity for the benzodiazepine receptor but have no intrinsic activity and are relatively free of side effects. Additionally, benzodiazepine antagonists cannot reverse the effects of anesthetic drugs (barbiturates) that bind to other sites on the $GABA_A$ receptor complex. Flumazenil is the only benzodiazepine antagonist currently available for clinical use. In animals, it is used primarily to reverse the sedative and muscle-relaxant effects of diazepam and other benzodiazepines.

Flumazenil

This is a highly selective, competitive benzodiazepine receptor antagonist. The chemical name of the drug is ethyl-8-fluro-5,6-dihydro-5-methyl-6-oxo-4H-imidazolo-(1,5-α)benzodiazepine-3-carboxylate (Fig. 9.16). Flumazenil has a strong affinity for the benzodiazepine receptor and has minimal intrinsic activity. The drug is used to reverse the unwanted behavioral and muscle relaxing effects of diazepam and midazolam in mammals and birds. Flumazenil is not approved for use in animals in Canada or the United States.

Pharmacokinetics and Pharmacodynamics Limited pharmacokinetic data are available for animals. An elimination half-life of 0.4 to 1.3 h has been reported for dogs.[320] In people, midazolam and flumazenil have similar pharmacokinetic profiles, which makes flumazenil a suitable antagonist for midazolam.[321] After IV administration, flumazenil is widely distributed and has an elimination half-life of approximately 1 h. The drug is not highly protein bound (<40%) and has a relatively high hepatic extraction ratio (0.6). Flumazenil undergoes hepatic metabolism and the primary metabolite is inactive.

Flumazenil rapidly reverses the sedative and muscle relaxant effects of benzodiazepine agonists in animals. In dogs, flumaze-

nil administration completely reverses the behavioral and muscle-relaxant effects of an overdose of diazepam (2 mg/kg IV) or midazolam (1 mg/kg IV) within 5 min.[320] In addition, flumazenil may reverse the anticonvulsant effects of benzodiazepine agonists. Although flumazenil has minimal intrinsic activity, administration of the antagonist could facilitate development of seizures in predisposed animals. Flumazenil also appears to have minimal effects on cardiopulmonary function in animals.

Clinical Uses Currently, flumazenil is the only benzodiazepine antagonist used in veterinary medicine. In dogs, an overdose of diazepam (2.0 mg/kg IV) or midazolam (1.0 mg/kg IV) can be effectively antagonized with flumazenil at a dose of 0.08 mg/kg.[320] These doses correspond to agonist/antagonist ratios of 26:1 and 13:1 for diazepam/flumazenil and midazolam/flumazenil, respectively. Flumazenil can be used in combination with opioid antagonists to reverse diazepam-oxymorphone sedation in dogs or alone to improve recoveries in cats given benzodiazepine-ketamine combinations.[322,323] In birds, flumazenil (0.1 mg/kg IM) has been used to reverse sedation and muscle relaxation induced by high doses of midazolam (2 to 6 mg/kg IM).[314] Following tiletamine-zolazepam (Telazol) administration in pigs, flumazenil can be used to reverse rear-limb muscle paralysis during recovery.

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