Anticholinergics

1. Atropine
2. Glycopyrrolate

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. **M1-**, **M2-** and **M3-muscarinic** cholinergic receptors

1. MI receptors are located on neurons in the central nervous system (CNS) and on autonomic ganglia.
2. M2 receptors are located in the sinoatrial (SA) andAV nodes and in the atrial myocardium.
3. M3 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.

- Salivary and bronchial glands are the **most sensitive** to muscarinic blockade.
- Cardiac tissues and smooth muscle are **intermediate** in sensitivity,
- Gastric parietal cells are **the least sensitive** to muscarinic blockade.

Peri operatively 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., α2-agonists and opioids).

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.

At therapeutic doses, nonselective muscarinic antagonists like atropine and glycopyrrolate reduce lower esophageal sphincter tone and have little effect on gastric pH. These two factors increase the incidence of **gastroesophageal reflux and esophagitis in anesthetized** dogs. Peri operative administration of anticholinergics also reduces intestinal motility and can lead to gastrointestinal complications postoperatively.

Atropine

Atropine is rapidly absorbed after intramuscular (1M) 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 I min, peak effects occur within 5 min, and heart rate increases by 30% to 40% for approximately 30 min. The effects of atropine on other body systems subside within a few hours.

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

therapeutic doses produces:

1. A mild sedative effect,
2. reduce the incidence of vomiting,
3. Mydriasis and cycloplegia,
4. Lacrimal secretions are also reduced which may contribute to corneal drying during anesthesia unless artificial tears are applied concurrently.
5. an acceleration of AV nodal conduction, and an increase in atrial contractility.
6. increase in vagal tone, Airway smooth muscle and secretory glands also receive parasympathetic input from the vagus nerves. 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.
7. Blockade of MI and M3 receptors in the gastrointestinal tract reduces secretory activity and motility.

Atropine is not usually administered peri operatively to large animals. Although it can be given to horses intraoperatively to manage severe bradycardia associated with administration of α 2agonists, gastrointestinal motility is reduced and colic can occur postoperatively

Clinical Uses

Atropine can be given subcutaneously (SC), 1M, or IV, but the 1M and IV routes are preferred because uptake from subcutaneous sites can be erratic in patients with altered hydration and peripheral 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.

Atropine is not usually given peri operatively to horses because of its gastrointestinal side effects.

Glycopyrrolate

Glycopyrrolate is four times as potent as atropine and has approximately the same affinity for all three major types of muscarinic receptors.

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.

Glycopyrrolate can be given intraoperatively to correct bradycardia in both small and large animals.

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 (aTagonists and opioids).
Glycopyrrolate can be given subcutaneously (SC), 1M, or IV, but the 1M and IV routes are preferred because uptake from SC sites can be erratic in patients with altered hydration and peripheral circulation.

Phenothiazines and Butyrophenones
The behavioral effects of these drugs are mediated primarily by blockade of dopamine receptors in the basal ganglia

Dopamine is largely an inhibitory neurotransmitter and is responsible for regulation of behavior, fine motor control, and prolactin secretion.

Acepromazine
This is one of the most widely used sedatives in veterinary medicine. 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.

Acepromazine administration produces dramatic effects on the cardiovascular system in both conscious and anesthetized animals.
Acepromazine administration produces significant gastrointestinal and urogenital effects.

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 apreanesthetic 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.

α2-Agonists

α2 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

Selective antagonists (tolazoline, yohimbine, and atipamezole)

Xylazine

Although its mechanism of action was unknown at the time of its introduction into clinical practice, xylazine was the first α2 agonist to be used by veterinarians.

In most species, the onset of sedation and analgesia is rapid after parenteral administration of xylazine

Xylazine administration decreases injectable and inhalational anesthetic requirements dramatically in several species.

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.

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.

Medetomidine

This is the most widely used a2-agonist in small animals.

It is more potent than xylazine and is dosed on a microgram-per-kilogram

Onset of sedation, analgesia, and muscle relaxation is rapid after 1M administration of medetomidine to dogs and cats, and the intensity and duration of these effects depend on dose.

Detomidine
This agent is used primarily for sedation and analgesia in horses.

Detomidine is more potent than xylazine and is dosed on a microgramper-kilogram basis rather than a milligram-per-kilogram basis.

Romifidine
This selective aragonist derived from clonidine is used primarily to produce sedation and analgesia in horses.

α'2-Antagonists
Tolazoline
This agent is a nonselective a-receptor antagonist used primarily to reverse the sedative and cardiovascular effects of xylazine in ruminants.

Yohimbine
This agent is used as a selective aTreceptor antagonist of the sedative and cardiovascular effects of xylazine in dogs, cats, and several exotic species

Atipamezole
This highly selective α2 receptor antagonist is used to reverse the sedative and cardiovascular effects of medetomidine in dogs, cats, and several other species

Benzodiazepine Agonists
Diazepam
This is the most widely used benzodiazepine in both small and large animals. Because of this insolubility, diazepam should not be mixed with diluents or other drugs. Further, the drug should not be administered 1M because it is very irritating and is poorly absorbed.

Diazepam does not sedate dogs and horses reliably, and can cause excitement, dysphoria, and ataxia.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.

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 used primarily as a peri operative sedative and muscle relaxant in ferrets, rabbits, swine, and birds.

Benzodiazepine Antagonists

Flumazenil
This is a highly selective, competitive benzodiazepine receptor antagonist.
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.