Acarbose

(ay-***kar***-bose) *Precose®, Glucobay®*

Antidiabetic Agent, Alpha Glucosidase Inhibitor

Prescriber Highlights

- ► Antihyperglycemic agent that reduces the rate and amount of glucose absorbed from the gut after a meal; may be useful in dogs and cats with mild hyperglycemia; unlikely to be effective when used as the sole therapy for management of diabetes mellitus
- ► Contraindications include a known hypersensitivity to the drug, diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or predisposition to obstruction, or chronic intestinal disease with marked disorders of digestion or absorption, as well as in patients that are underweight or in cases in which excessive GI gas formation would be detrimental.
- ► Adverse effects can limit the drug's usefulness and include dose-dependent loose stools, diarrhea, and flatulence.
- ► Give with meals (preferably right before feeding); this drug is not as effective if feeding ad libitum.

Uses/Indications

Acarbose may be useful in reducing blood glucose concentrations in cases of mild to moderate hyperglycemia (250-350 mg/dL range) in dogs and cats with non-insulin-dependent diabetes mellitus and as adjunctive treatment for insulin-dependent diabetes mellitus. Acarbose may be useful in dogs or cats when insulin activity peaks too soon.[1]

In healthy cats, acarbose resulted in a 5% to 7.5% reduction in postprandial glucose area under the curve (AUC) and a 35% to 45% reduction in postprandial insulin AUC as compared to no treatment.[2] In diabetic cats, acarbose apparently is most effective in cats that refuse to eat a low carbohydrate diet and consume their food within a short time after acarbose is given. Acarbose given in conjunction with a high carbohydrate diet has an effect similar to feeding an ultra-low carbohydrate diet.[3] Acarbose is usually not effective in animals with reduced appetites (eg, cats with advanced chronic kidney disease). Acarbose may be considered in dogs when glycemic control is poor and the cause is not determined.[4] Acarbose is unlikely to give adequate glucose control when used alone; dietary therapy and other antihyperglycemic agents (eg, insulin) are typically recommended instead.

Pharmacology/Actions

Acarbose competitively inhibits pancreatic alpha-amylase and alpha-glucosidases found in the small intestine. This inhibition delays the digestion of complex carbohydrates and disaccharides to glucose and other monosaccharides, which causes glucose to be absorbed in lesser amounts lower in the GI tract. This reduced absorption decreases blood glucose and insulin requirements during the postprandial hyperglycemic phase. Acarbose has no effect on lactase nor does it enhance insulin secretion.

Pharmacokinetics

In dogs, ≈4% of an oral dose is absorbed; in humans, only ≈2% of an oral dose is absorbed from the gut and then excreted by the kidneys. Practically all of the remaining drug in the gut is metabolized by intestinal bacterial flora. Patients with severe renal dysfunction attain serum levels ≈5 times those of normal patients.

Contraindications/Precautions/Warnings

Acarbose is contraindicated in patients with known hypersensitivity to the drug, diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or predisposition to obstruction, and chronic intestinal disease with marked disorders of digestion or absorption, as well as when excessive GI gas formation would be detrimental. Acarbose is contraindicated in patients with low body weight (may also apply to patients with normal body weight), as the drug may have deleterious effects on nutrition status. Use caution in patients with renal dysfunction or severe liver disease.

Adverse Effects

Adverse effects reported in cats include flatulence, soft stools, and diarrhea. In dogs, adverse effects include soft or watery stools, diarrhea, and weight loss.[4] These adverse effects are more likely at higher doses and may outweigh treatment benefits.[5]

Although acarbose alone does not cause hypoglycemia, it may contribute to it by reducing the rate and amount of glucose absorbed when the patient is receiving other hypoglycemic agents (eg, insulin, oral hypoglycemic drugs).

Dose-related increases in hepatic transaminases have been reported rarely in humans.

Reproductive/Nursing Safety

Studies in laboratory animals have demonstrated no evidence of fetal harm or impaired fertility. Weigh any potential risks versus benefits in pregnant animals.

It is not known if acarbose is excreted in maternal milk. Acarbose is likely safe to use during nursing because it is minimally absorbed.

Overdose/Acute Toxicity

Acute overdoses are likely to only cause diarrhea and flatulence; no treatment should be necessary. If acute hypoglycemia occurs secondary to other hypoglycemic agents, parenteral glucose should be administered. Use glucose (eg, dextrose) instead of sucrose when treating orally, as the absorption of oral glucose is not inhibited by acarbose.

For patients that have experienced or are suspected to have experienced an overdose, it is strongly encouraged that a 24-hour poison consultation center that specializes in providing information specific for veterinary patients be consulted. For general information related to overdose and toxin exposures, as well as contact information for poison control centers, refer to ***Appendix***.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving acarbose and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Charcoal, Activated**: Intestinal adsorbents may reduce the efficacy of acarbose.
- **Digoxin**: Acarbose may reduce digoxin blood concentrations.
- **Hyperglycemic Agents** (eg, **calcium channel blockers, corticosteroids, estrogens, phenothiazines, thiazides, thyroid hormones**): May reduce or negate the effects of acarbose
- **Hypoglycemic agents** (eg, **insulin, sulfonylureas**): May increase the risk for hypoglycemia
- **Pancreatin, Pancrelipase,** or **Amylase**: Exogenous enzyme formulations may reduce the efficacy of acarbose.

Laboratory Considerations

- Increased serum aminotransferase (ALT) and bilirubin levels have been noted in some humans taking high dosages for a long period.

Dosages

DOGS:

Adjunctive treatment for diabetes mellitus (extra-label): Initially, 12.5 – 25 mg/dog (NOT mg/kg) PO with each meal (usually twice daily). Give only at time of feeding (right before). If response is in-

adequate after 2 weeks, the dosage may be titrated up to 50 mg/dog (NOT mg/kg) PO twice daily. For dogs weighing greater than 10 to 25 kg (22 to 55.1 lb), a further increase up to 100 mg/dog (NOT mg/kg) twice daily may be considered if response has been inadequate.

CATS:

Adjunctive treatment for diabetes mellitus (extra-label): 12.5 mg/cat (NOT mg/kg) PO twice daily with a meal.[2,3,6,7] One study found acarbose to be ineffective in healthy cats fed a low carbohydrate diet.[6]

Monitoring

- Serum glucose
- Adverse effects (eg, diarrhea, flatulence)
- Liver enzymes

Client Information

- For best results, give this drug right before feeding your animal. Tablets may be split or crushed and mixed with food just prior to administration.
- Diarrhea and/or gas are the most likely side effects.
- Acarbose does not cause low blood sugar; however, it may contribute to it if the animal is getting other drugs that lower blood sugar (including insulin). Call your veterinarian immediately if you see signs of low blood sugar (eg, seizures [ie, convulsions], collapse, rear leg weakness or paralysis, muscle twitching, unsteadiness, tiredness, depression).
- It may take up to 2 weeks for the drug to work.

Chemistry/Synonyms

Acarbose, a complex oligosaccharide antihyperglycemic agent, occurs as a white to off-white powder, is soluble in water, and has a pK_a of 5.1.

Acarbose may also be known as Bay-g-5421, *Asucrose®*, *Glicobase®*, *Glucobay®*, *Glucor®*, *Glumida®*, *Prandase®*, or *Precose®*.

Storage/Stability

Do not store tablets above 25°C (77°F), and protect them from moisture.

Compatibility/Compounding Considerations

Tablets may be split or crushed and mixed with food just prior to administration.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: NONE

HUMAN-LABELED PRODUCTS:

Acarbose Oral Tablets: 25 mg, 50 mg, and 100 mg; *Precose®*, generic; (Rx)

References

For the complete list of references, see **wiley.com/go/budde/plumb**

Acepromazine

Acetylpromazine

(***ase***-pro-ma-zeen) *PromAce®*

Phenothiazine Sedative/Tranquilizer

Prescriber Highlights

- ► Used as a sedative/tranquilizer, or in balanced anesthetic or analgesic protocols; also used as adjunctive treatment of urethral obstruction in male cats and laminitis in horses
- ► Clinical dosages are significantly lower than those listed on the United States-approved label.
- ► Time to onset (15 minutes, up to 30 minutes for full effect) and duration of action (3 to 4 hours, up to 6 to 8 hours in some animals) are relatively long as compared with other sedatives such as the alpha-2 agonists.
- ► Does not have a reversal agent
- ► Provides no analgesic effects but can be combined with analgesics (eg, opioids) to enhance sedation and increase duration of analgesia (ie, neuroleptanalgesia). Use a low dose of acepromazine when combining with other sedatives or anesthetic drugs.
- ► Acepromazine has minimal to no impact on respiratory function but may cause significant hypotension and hypothermia; it should be avoided or dose-reduced in debilitated animals, especially those with predicted or pre-existing hypotension or hepatic insufficiency; and used with caution in patients with moderate to severe cardiac disease that cannot tolerate reduced blood pressures.
- ► Dogs with the multidrug sensitivity gene *(MDR1) mutation (also known as ABCB1-*1delta) are overly sensitive to effects and require dose reduction or avoidance.
- ► Use with caution as a sole sedative in aggressive dogs as dogs may be prone to startling and occasional dogs experience worsening of aggression and CNS stimulation.
- ► May cause penile prolapse in horses, but associated permanent penile dysfunction is very rare.

Uses/Indications

Acepromazine is FDA-approved for use in dogs, cats, and horses. Labeled indications for dogs and cats include as an aid in controlling intractable animals and alleviating itching as a result of skin irritation, as an antiemetic to control vomiting associated with motion sickness, and as a preanesthetic agent.[1]

Acepromazine has a wide safety margin and is one of the most commonly used sedatives/tranquilizers in small animal species, with less frequent use in large animal species. The injectable formulation is used primarily as a preanesthetic agent or for procedural sedation. Sedation with acepromazine is mainly indicated for use in healthy patients or patients with mild systemic disease. Because acepromazine has minimal effects on respiratory function, it can be a useful tranquilizer/sedative in small animal species with upper airway obstruction (eg, laryngeal paralysis). The long duration of action can be advantageous in some situations (eg, can promote smoother recovery from anesthesia in excited/anxious animals) but can be problematic in others (eg, can delay discharge in same-day sedation/anesthesia procedures).

Acepromazine has been used as one part of a multimodal protocol to resolve urethral obstruction in male cats without the need for urethral catheterization[2]; this protocol may be beneficial in situations where client financial constraints limit treatment and would otherwise result in euthanasia.

Acepromazine has no analgesic effects; however, when combined with opioid analgesics, acepromazine can enhance sedation and pro-

long the opioid analgesic effect (neuroleptanalgesia). Acepromazine also has antihistamine and antiemetic effects; however, it is not commonly used for these indications due to availability of more specific and effective treatment options.

The oral form of acepromazine is most commonly used to decrease an animal's response to stress or fear-inducing stimuli like loud noises (eg, fireworks, thunder) or travel. Whether acepromazine causes anxiolysis or only sedation in these situations is unknown and controversial. Specific drugs that cause fewer adverse effects are available for behavioral modification associated with anxiety in dogs and cats.

In horses, acepromazine is labeled for use as an aid in controlling fractious animals and in conjunction with local anesthesia for various procedures and treatments.[1] It is also commonly used in horses at low doses (0.005 – 0.04 mg/kg) as a preanesthetic agent for mild sedation and for its potential antiarrhythmic effects.[3] Acepromazine has also been administered to horses with laminitis to improve blood flow to the distal limb.[4–6]

Although not FDA-approved, acepromazine is used as a tranquilizer in other species such as cattle, sheep, goats, swine, and rabbits. Acepromazine has been shown to reduce the incidence of halothane-induced malignant hyperthermia in susceptible pigs.[7]

Pharmacology/Actions

Acepromazine is a phenothiazine neuroleptic agent. Although the exact mechanisms of action are not fully understood, phenothiazines block postsynaptic dopamine receptors in the CNS and may inhibit the release of dopamine and increase its turnover rate. They are thought to depress portions of the reticular activating system that assist in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness. In addition, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects.

The primary desired effect for the use of acepromazine in veterinary medicine is tranquilization/sedation. Additional desirable pharmacologic actions of acepromazine include its use as a muscle relaxant, antiemetic, antiarrhythmic (blockade of myocardial alpha-1 receptors), and antispasmodic. Examples of muscle relaxant/antispasmodic effects include relief of clinical signs in a mare with urethral spasms[8] and reduction of urethral pressure in cats anesthetized with halothane.[9]

Vasodilation secondary to alpha-1 receptor blockade can contribute to hypotension with potential reflex tachycardia; however, mild vasodilation can be beneficial in some dogs and cats with cardiac disease in which systemic vasodilation or a decrease in afterload is desired, as in moderate to severe mitral regurgitation. In this case, acepromazine 0.005 – 0.01 mg/kg is adequate. A combination of acepromazine and an opioid is commonly used for sedation of patients for cardiac imaging because of the limited to no impact on cardiac function. In one study, acepromazine 0.02 mg/kg combined with butorphanol 0.2 mg/kg administered IM to dogs provided adequate sedation for echocardiography with only mild changes on measured variables.[10] In dogs, premedication with acepromazine caused a moderate decrease in blood pressure without significantly altering glomerular filtration rate or renal blood flow.[11]

Acepromazine may decrease respiratory rate, but studies have demonstrated that little or no effect occurs with regard to blood gas status, pH, and/or oxyhemoglobin saturation.[12–15]

A dose-dependent decrease in hematocrit can be seen within 30 minutes after administration to dogs and horses. Hematocrit values in horses may decrease ≈20% of predose values; this change is due to increased splenic sequestration of red blood cells, which has been demonstrated in dogs.[13,16–18] Although the red blood cells return to circulation, this effect may not occur until after recovery from anesthesia and could exacerbate decreased oxygen delivery during anesthesia of anemic patients. Acepromazine may transiently reduce platelet count and aggregation; however, platelet function and hemostasis are not altered.[19,20]

Although acepromazine use was historically avoided in epileptic animals and in those that were susceptible to seizures (eg, postmyelography), recent research has disproved this effect and shown that acepromazine may have some anticonvulsant activity. In a study, acepromazine did not significantly alter EEG in healthy dogs.[21] In other studies, acepromazine caused no seizures, even in high-risk dogs, and actually decreased seizures in some actively convulsing dogs.[22–24]

Acepromazine can delay gastric emptying, reduce lower esophageal tone, and slow GI motility in dogs, cats, horses, cattle, and likely other species.[25–28] This effect is not likely to have a clinical impact in most animals but could influence GI motility studies[25] and potentially increase the risk for gastric reflux.

Other pharmacologic actions are discussed in the ***Adverse Effects*** section.

Pharmacokinetics

In dogs that receive acepromazine 1.3 – 1.5 mg/kg, oral bioavailability is ≈20% and elimination half-lives are ≈7.1 hours (IV) and 16 hours (PO).[29]

In horses, acepromazine 0.3 mg/kg IV has a fairly high volume of distribution (6.6 L/kg) and is more than 99% protein bound.[17] The onset of action is fairly slow, requiring up to 15 minutes following IV administration, with peak effects seen in 30 to 60 minutes. Elimination half-life is ≈3 hours. In one study, horses appeared sedated (based on chin-to-ground measurement) within 5 minutes of IV administration as compared with 15 minutes for oral and sublingual administration (0.09 mg/kg for all routes); sedation lasted 2 hours.[30] Elimination half-lives after oral, sublingual, and IV administration were 8.6 hours, 6.7 hours, and 5.2 hours, respectively.

Acepromazine is metabolized in the liver with both conjugated and unconjugated metabolites eliminated in the urine.[1,31] Metabolites may be found in equine plasma up to 24 hours and urine up to 144 hours after IV administration.[32]

Contraindications/Precautions/Warnings

Acepromazine potentiates the toxicity of organophosphates (including those found in flea collars) and procaine hydrochloride, and it is contraindicated in patients that are receiving or exposed to those agents.[1] There are no other absolute contraindications.

In the United States, the parenteral formulation is only available as a 10 mg/mL concentration. Dilution of the drug or use of very small syringes (eg, tuberculin syringes, U-100 insulin syringes) is important for safe administration to small animal patients. For instance, at a dose of 0.03 mg/kg, a 10-kg (22-lb) dog would receive 0.03 mL of 10 mg/mL acepromazine.

In all species, the tranquilization effects of acepromazine can be overridden by patient arousal, so it cannot always be relied on when used alone as a restraining agent. The effects of acepromazine may be individually variable and breed dependent. Animals will require lower doses of general anesthetics after receiving acepromazine. This is a dose-dependent effect that is true for all species and all inhalant anesthetics in current clinical use.

Acepromazine has no analgesic effects; animals should be treated with appropriate analgesics to control pain. Sedation of painful patients without provision of analgesia can result in the inability to identify pain behaviors with a subsequent negative impact on animal health and welfare.

Acepromazine does not have a reversal agent and requires hepatic metabolism for termination of effect; thus, it should either not be used or should be used cautiously at the low end of the dose range in animals with moderate hepatic dysfunction (eg, some geriatric and pediatric patients) and avoided if the disease/dysfunction is severe.[1,33]

Because of its potential hypotensive effects, acepromazine should either not be used or be used cautiously at the low end of the dose range in patients with mild cardiac disease that may not tolerate drops in blood pressure or in those with decreased sympathetic nervous system response to hypotension (eg, general debilitation, obtundation, neonates, some pediatric and geriatric patients) and avoided in patients with significant cardiac disease, hypovolemia, dehydration, hypotension, or shock.[1,33]

Acepromazine may decrease platelet aggregation and should be avoided or used with caution in patients with coagulopathies or thrombocytopenia.[19,20] Use acepromazine with caution in anemic animals, as splenic red blood cells will exacerbate signs associated with the anemic condition.[34] Acepromazine-mediated splenic engorgement (see ***Pharmacology/Actions***) can make performing a splenectomy difficult; consider other premedication agents for this surgery.

In all species, IV injections should be administered slowly,[1] which is recommended for most sedatives/anesthetic agents to avoid sudden profound sedation or paradoxical excitement. Acepromazine should not be administered intra-arterially, as it may cause severe CNS excitement/depression, seizures, and death.

Acepromazine's vasodilatory effects may be deleterious in compromised horses (eg, acute colic, cantharidin toxicosis, dehydration/hypovolemia, hypotension/shock). In a study of healthy horses, IV infusion of norepinephrine at 1 µg/kg/minute reversed the hypotensive effects of 0.1 mg/kg acepromazine IV.[35]

Breed-specific concerns include dogs with *MDR1* gene mutation (also known as *ABCB1*-1delta), which may develop a more pronounced sedation that persists longer than expected.[36] The drug is best completely avoided in *MDR1*-mutant dogs because there is no reversal, but if no other option is available, the dose should be reduced by 25% in dogs that are heterozygous and by 30% to 50% in dogs that are homozygous for the *MDR1* gene mutation (mutant/mutant).[36,37] Spontaneous fainting or syncope due to sinoatrial block caused by excessive vagal tone has been observed in some dogs, particularly boxers and other brachycephalic breeds; a low acepromazine dose should be used with or without atropine in these patients.[38] **NOTE**: This issue has only been reported in boxers (and *not* other brachycephalic breeds) and may be present in a familial line, as it is rarely reported, especially outside the UK. When there is a history of this type of syncope, or if it is suspected because of excessive sinus arrhythmia, it may be advantageous to control the dysrhythmia with atropine administered just before the acepromazine.[38]

Acepromazine should be used very cautiously as a restraining agent in aggressive dogs, as it may make the animal more prone to startle and react to noises or other sensory inputs and can potentially make them more aggressive; it is best used in combination with other restraining agents in these situations. In some geriatric patients, very low doses have been associated with prolonged effects of the drug, likely due to slowed hepatic metabolism. Anecdotally, giant breeds appear to be sensitive to the drug, whereas terrier breeds appear to be somewhat resistant to its effects; however, this is most likely based on use of body weight instead of body surface area for dose calculation.[34]

Adverse Effects

The potential for acepromazine-mediated hypotension and possible reflex tachycardia should be considered during treatment planning. This effect is mediated by central mechanisms and through the alpha-adrenergic antagonistic action of the drug. Secondary tachycardia may accompany the hypotension.[1] Cardiovascular collapse (secondary to bradycardia and hypotension) can occur after rapid IV injection[1] and has been reported in dogs following IM administration of supraclinical doses (1 mg/kg).[39] Atropine may be used to treat this effect.[38] Splenic sequestration of red blood cells may cause transient decreases in PCV. See ***Pharmacology/Actions***.

Occasionally, an animal may develop the contradictory clinical signs of aggressiveness and generalized CNS stimulation after receiving acepromazine. For orally administered acepromazine tablets, mild respiratory distress (ie, reverse sneeze) has been reported and does not have an effect on the desired action of the drug.

Acepromazine causes prolapse of the nictitating membrane and has been shown to decrease tear production in cats[40] and rabbits.[41]

In horses, acepromazine may cause protrusion of the penis; this effect is dose-related and may last for 2 or more hours.[17] Permanent penile dysfunction in horses and ponies is possible, but a retrospective study found the risk to be extremely low (less than or equal to 1 in 10,000).[42] The main contributor to permanent penile dysfunction is prolonged protrusion and subsequent penile edema followed by inability to retract the penis and worsening edema. If using acepromazine in male horses, ensure penile retraction occurs within 1 hour of protrusion.

Acepromazine inhibits the voltage-gated K+ channel (Kv11.1), which may induce repolarization disorders and lead to drug–drug interactions that prolong the QT interval[43]; however, this seems to have no clinical impact.

IM administration may cause transient pain at the injection site, which is possibly related to the injection itself rather than the drug. SC administration may be less painful than IM while providing similar sedation.[44]

In addition to the legal aspects (ie, extra-label; not FDA-approved) of using acepromazine in cattle, the drug may cause regurgitation of ruminal contents when sedation is followed by general anesthesia.

Reproductive/Nursing Safety

Acepromazine injection is listed as contraindicated in pregnant animals on at least one international drug label[38]; however, acepromazine has been used safely in late-term pregnant cattle[45] and ferrets.[46] Use of the drug in cesarean sections in dogs and cats is not recommended because of the prolonged duration of recovery and potential for hypotension. Excretion of the drug in milk has not been evaluated; however, acepromazine has been used in mares to promote lactation (secondary to increased prolactin production) and facilitate adoption of orphan foals. In one case report, acepromazine (30 mg IM every 8 hours for 48 hours) administered to a thoroughbred mare increased milk production, calmed the mare, and promoted bonding with an orphan foal while having no impact on the mare's concurrent pregnancy.[47]

Because safety has not been established in animals, this drug should only be used when the maternal benefits outweigh the potential risks to offspring.

Overdose/Acute Toxicity

LD_{50} in mice is 59 mg/kg after IV administration, 130 mg/kg after SC administration, and 200 mg/kg after oral administration.[48] A toxicity study in dogs reported no adverse effects in dogs receiving 20 – 40 mg/kg over 6 weeks[1]; however, anecdotally, adverse effects have been reported in dogs receiving single doses between 20 and 42 mg/kg. Dogs have survived oral doses up to 220 mg/kg, but overdoses can cause severe hypotension, CNS depression, pulmonary edema, and/or hyperemia of the internal organs.[1] Acepromazine overdose can also cause extrapyramidal effects (eg, tremor, catalepsy, rigidity, excitement, sweating, seizures) via dopamine blockade.[49]

Because of the relatively low toxicity of acepromazine, most overdoses can be handled by monitoring the animal and treating clinical signs as they occur; massive oral overdoses should be treated by gastric decontamination if possible. Hypotension should be treated initially with IV fluids; alpha-adrenergic pressor agents (eg, norepi-

nephrine, phenylephrine; *not* epinephrine) can be considered if IV fluid therapy does not maintain adequate blood pressure. **NOTE**: Epinephrine is contraindicated for treatment of acute hypotension produced by phenothiazine-derivative tranquilizers since further depression of blood pressure can occur.[1,33] This phenomenon is known as epinephrine reversal and could occur when epinephrine is administered after an alpha-adrenergic antagonist (eg, acepromazine). In these situations, the peripheral beta-adrenergic effects of epinephrine will predominate, resulting in relaxation of the vascular smooth musculature and hypotension.

Seizures may be controlled with benzodiazepines. Doxapram has been suggested as an antagonist to the CNS depressant effects of acepromazine, and one study in dogs found that doxapram 1.25 mg/kg IV significantly reduced sedation scores and did not induce panting.[50] See ***Doxapram***.

For patients that have experienced or are suspected to have experienced an overdose, consultation with a 24-hour poison consultation center specializing in providing veterinary-specific information is recommended. For general information related to overdose and toxin exposures, as well as contact information for poison control centers, refer to ***Appendix.***

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving acepromazine or other phenothiazines and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but the potential risks should be weighed, and additional monitoring performed when appropriate.

- **Alpha-2 Agonists** (eg, **dexmedetomidine, xylazine**): Additive risk for CNS depression when used with acepromazine
- **Anesthetic Agents** (eg, **alfaxalone**, **isoflurane, ketamine**): Additive CNS depression is possible.
- **Antipyretics** (eg, **acetaminophen, dipyrone, NSAIDs**): Possible increased risk for hypothermia with concurrent use
- **Antacids, Aluminum-, Calcium- or Magnesium-Containing**: Concomitant use of acepromazine or other phenothiazines with antacids may cause reduced GI absorption of oral phenothiazines; administration should be separated by at least 2 hours to minimize this effect (with acepromazine being administered before the antacid).[51]
- **Anticholinergic Agents** (eg, **atropine, glycopyrrolate, hyoscyamine**): Increased risk of anticholinergic effects (eg, dry mucous membranes, constipation, urinary retention)
- **Antidiarrheal Mixtures** (eg, **bismuth subsalicylate, kaolin/pectin**): Concomitant use of acepromazine or other phenothiazines with antidiarrheal mixtures may reduce GI absorption of oral phenothiazines; administration should be separated by at least 2 hours to minimize this effect (with acepromazine being administered before the antidiarrheal mixture).[51]
- **Barbiturates** (eg, **pentobarbital, phenobarbital**): Causes additive CNS depression when used with acepromazine. Although this effect is desirable when the 2 drugs/drug classes are used for anesthesia or euthanasia, it may not be desirable if the barbiturates are being used for seizure control in conscious patients.
- **Benzodiazepines** (eg, **diazepam, midazolam**): Additive risk for CNS depression when used with acepromazine
- **Cannabidiol**: Additive risk for CNS depression
- **Cimetidine:** Cimetidine may increase chlorpromazine concentrations; no information for structurally related acepromazine, but combination could lead to excessive sedation and hypotension. Avoid combination if possible.
- **Cisapride:** Concurrent use with acepromazine and other phenothiazines may increase risk for QT interval prolongation, cardiac arrhythmias, torsade de pointes, and death. Acepromazine may reduce prokinetic effect of cisapride. Concurrent use of cisapride with acepromazine or other phenothiazines should be avoided.
- **Dopaminergic Agonists** (eg, **bromocriptine, cabergoline, pergolide**): Concurrent use may reduce the efficacy of both drugs and should be avoided
- **Emetics** (eg, **apomorphine, ropinirole**)**:** Acepromazine may reduce the effectiveness of emetics as well as increased risk for sedation and hypotension.
- **Epinephrine:** Contraindicated in the treatment of acute hypotension produced by acepromazine or other phenothiazines, as further depression of blood pressure can occur (also referred to as epinephrine reversal)
- **Fluoxetine**: May increase chlorpromazine concentration in humans due to inhibition of CYP2D6; the relevance of this interaction for acepromazine use in veterinary species is uncertain
- **Hypotensive Agents** (eg, **amlodipine, benazepril, enalapril, telmisartan**)**:** Concurrent use of acepromazine with hypotensive agents may increase risk for hypotension; monitor blood pressure.
- **Methocarbamol:** Concurrent use may cause additive CNS depression.
- **Metoclopramide**: Concurrent use may increase risk for extrapyramidal adverse effects (eg, tremor, catalepsy, rigidity, excitement, sweating, seizures). Acepromazine may reduce prokinetic effect of metoclopramide.
- **Opioids** (eg, **buprenorphine, fentanyl, morphine**): May enhance the hypotensive effects of the phenothiazines; dosage of acepromazine may need to be reduced when used with an opioid
- **Organophosphate Agents**: Acepromazine should not be given within one month of treatment with or accidental exposure to these agents as organophosphate toxicity may be potentiated.
- **QT Prolonging Agents** (eg, **cisapride, domperidone, erythromycin, sotalol**): Concurrent use may increase risk for QT prolongation and should be avoided.
- **Procaine**: Although not clinically documented, procaine activity may be enhanced by phenothiazines and some resources state that concurrent use with acepromazine is contraindicated.[1,33]
- **Propranolol**: Increased blood concentrations of both propranolol and acepromazine may result if administered concurrently.
- **Quinidine**: Concurrent use with acepromazine or other phenothiazines may cause additive cardiac depression.
- **Sucralfate:** May reduce GI absorption of oral phenothiazines

Laboratory Considerations

- Acepromazine does not alter the results of **glucose tolerance testing** in dogs.[52]
- Because acepromazine has antihistamine effects, it can decrease the wheal-and-flare response to antigens during **intradermal skin testing**. In dogs and cats, it has been suggested that antihistamines be discontinued at least 2 weeks before testing.[53]

Dosages

NOTES:

1. Acepromazine does not provide analgesia; addition of an analgesic agent is required when pain relief is needed.
2. Administer IV doses slowly; allow at least 15 minutes for onset of action.[1]

DOGS & CATS:

NOTE: The label dosage for dogs and cats is considered by most clinicians to be 10 to 100 times (or more) greater than is necessary for most indications. The labeled indications are provided below, but the use of lower, extra-label dosages is strongly recommended.

Dogs: **As an aid in tranquilization, controlling intractable ani-**

mals, and alleviating itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness; and as a preanesthetic agent (label dosage; FDA-approved): 0.55 – 2.2 mg/kg PO (dose may be repeated as required), or 0.55 – 1.1 mg/kg IV, IM, or SC[1,33]

Cats: **As an aid in controlling intractable animals and alleviating itching as a result of skin irritation, as an antiemetic to control vomiting associated with motion sickness, and as a preanesthetic agent** (label dosage; FDA approved): 1.1 – 2.2 mg/kg IV, IM, or SC[1]

Sedation, tranquilization, premedication, or restraint (extra-label):

1. Injectable: 0.01 – 0.1 mg/kg IV (slowly), IM, or SC generally as a single dose but could be repeated if initial dose is ineffective or after sedative effects have dissipated and continued sedation is desired. Maximum sedation in most patients likely occurs at 0.05 mg/kg.[34] Numerous anesthesia references recommend that total dose should not exceed more than 3 mg (total dose/dog; NOT mg/kg)[54,55]; however, some references recommend a maximum dose of 4 mg (total dose/dog; NOT mg/kg).[38,56] This is especially true in large breed dogs[55] who appear more "sensitive" to higher dosages of acepromazine, which is actually due to dosing on a mg/kg basis rather than on a body surface area basis.[34]
   a. Anesthetic premedication: 0.02 – 0.05 mg/kg IM, SC, or slow IV. Lower doses (ie, 0.02 – 0.03 mg/kg) are sufficient for most patients, especially when the drug is combined with an opioid. The lower end of the dosing range should be used for IV administration. Following acepromazine administration, anesthetic induction agent doses can often be reduced by ≈30%.
   b. Tranquilization/sedation: 0.03 – 0.125 mg/kg IM, SC, or slow IV.[38] Dosages in the preanesthetic range are often sufficient, especially when combined with an opioid. The lower end of the dosing range should be used for IV administration. Lower doses should be used for tranquilization and higher doses used for sedation. Typically administered as a single dose but could be repeated if initial dose was ineffective or after sedative effects have dissipated and continued sedation is desired; long-term use is not recommended.
2. Oral: Anecdotal dose recommendations vary widely but generally these are similar to the labeled dose range of 0.55 – 2.2 mg/kg PO, although some clinicians think that doses at the higher end of this range are too high. If oral doses require repeating, they are usually given every 6 to 12 hours. Acepromazine also may be given in combination with an anxiolytic medication (eg, gabapentin, trazodone).
3. Transmucosal (TM)
   a. Sedation for cats (anecdotal): Using injectable formulations, 0.05 – 0.1 mg/kg combined with buprenorphine 0.03 mg/kg and administered TM 30 to 90 minutes prior to appointment
   b. Sedation for dogs: Acepromazine 0.025 – 0.05 mg/kg OTM should be administered 30 minutes before the scheduled appointment given in combination with an anxiolytic medication (eg, gabapentin, trazodone), as in the "Chill Protocol" in which the animal receives gabapentin ≈12 hours prior to leaving the home for the veterinary hospital and melatonin and gabapentin PO ≈ 2 hours prior.[57]

Adjunctive treatment of urethral obstruction in male cats (extra-label): 0.25 mg/cat (NOT mg/kg) IM OR 2.5 mg/cat (NOT mg/kg) PO every 8 hours in combination with medetomidine 0.1 mg IM every 24 hours and buprenorphine 0.075 mg PO every 8 hours.[2] Acepromazine is not recommended in obtunded cats as profound hypotension and hypoventilation could occur. See ***Contraindications/Precautions/Warnings***.

HORSES:

As an aid in controlling fractious animals and in conjunction with local anesthesia for various procedures and treatments (label dosage; FDA-approved): 0.044 – 0.088 mg/kg (2 – 4 mg/100 lb [45 kg] body weight) IV (slowly), IM, or SC[1]

Sedation, tranquilization, premedication (extra-label): When used alone, acepromazine is usually dosed similarly to the label: 0.02 – 0.1 mg/kg IM, IV, or SC. When used in combination with drugs such as butorphanol as a premedication or to increase blood flow in the treatment of laminitis, recommended doses are usually on the low end of this range. Repeat doses should be limited and ideally not given more frequently than every 36 hours.

Anesthetic premedication, to facilitate restraint, or for sedation during travel (extra-label): Preanesthetic: 0.02 – 0.05 mg/kg IM or slow IV; sedation/restraint: 0.05 – 0.1 mg/kg IM or slow IV. Administer up to 15 minutes prior to the desired effect and await clinical signs of tranquilization before travel or subsequent administration of anesthetic. The low end of the dose range is generally adequate. For tranquilization, adjust dose to maintain desired effect for the duration of travel or procedure.[58,59] These doses can also be used to sedate mares during extended separation from their foals.

Sedation in donkeys: 0.1 mg/kg IV produced sedation ≈10 minutes after administration, which lasted ≈80 minutes.[60,61] In general, horse doses are appropriate for donkeys, but the higher end of the dose range may be necessary to adequately sedate mules.

Laminitis (extra-label): 0.04 – 0.066 mg/kg IM, IV, or SC[5,6,62]

CATTLE:

All dosages are extra-label.

a) **Sedation**: 0.01 – 0.02 mg/kg IV or 0.03 – 0.1 mg/kg IM[63]
b) **Mild sedation or tranquilization**: 0.02 – 0.05 mg/kg IV, 0.02 – 0.1 mg/kg IM[64]
c) **Sedative 1 hour before local anesthesia**: 0.1 mg/kg IM[64]

SHEEP & GOATS:

Sedation (extra-label): 0.05 – 0.1 mg/kg IM.[65] Sedation in sheep was equivalent when acepromazine 0.03 mg/kg IM was administered either with morphine 0.3 mg/kg IM or buprenorphine 0.02 mg/kg IM.[66] The low end of the dose is generally adequate.

SWINE:

NOTE: When used as a single agent in swine, the effects of acepromazine are inconsistent and may be inadequate.

Sedation (extra-label)**:**

a) 0.1 – 0.2 mg/kg IV, IM,[67] or SC[68]
b) 0.03 – 0.1 mg/kg IM[65,69]

Brief periods of immobilization (extra-label)**:** Acepromazine 0.5 mg/kg in combination with ketamine 15 mg/kg IM.[67] Atropine 0.044 mg/kg IM will reduce salivation and bronchial secretions.[70]

FERRETS:

All dosages are extra-label.

a) **Tranquilization**: 0.25 – 0.75 mg/kg IM or SC[46] ; the lower to mid-range of the dosage is generally adequate.
b) **Premedication**: 0.1 – 0.25 mg/kg IM or SC; may cause hypotension/hypothermia[71]

RABBITS, RODENTS, & SMALL MAMMALS:

All dosages are extra-label.

a) **Rabbits: Sedative/tranquilization**: 0.75 – 1 mg/kg IM. Effect should begin 10 minutes after administration and last for 1 to 2 hours.[63,72]

b) **Rabbits: Premedication**: 0.2 – 1 mg/kg SC, IM[73,74]
c) **Mice, rats, hamsters, guinea pigs, chinchillas**: 0.5 – 1.5 mg/kg IM, SC; 0.5 – 2.5 mg/kg PO. Can be used IP in some species. Use in gerbils is not recommended by some clinicians.[75]

Monitoring

- Cardiac rate and rhythm, blood pressure (critical), end-tidal carbon dioxide ($ETCO_2$), and pulse oximetry (recommended)
- PCV and total protein, especially in borderline anemic patients and patients with current or expected blood loss
- Degree of sedation/tranquilization
- Male horses should be checked to make sure the penis retracts and is not injured.
- Body temperature (especially if ambient temperature is very hot or cold)

Client Information

- This medicine will have the best effect when it is given by mouth 45 to 60 minutes before the procedure or travel. Sedative or tranquilizing effects (sleepiness) and side effects may last up to 24 hours. Your veterinarian may recommend a trial dose a few days before travel to see how your animal reacts to the medicine.
- Animals sedated with this medicine may startle easily in response to sounds or other sudden stimuli. Use caution when approaching your animal as this effect can occasionally make them more aggressive. If this occurs, isolate your animal in a safe environment and contact your veterinarian.
- Keep treated animal in a quiet environment at a comfortable temperature.
- This medicine may cause a harmless pinkish to reddish-brown discoloration of your animal's urine. This change is not to be worried about.
- Do not give additional medicines to tranquilize or sedate your animal unless instructed to do so by your veterinarian.

Chemistry/Synonyms

Acepromazine maleate (formerly acetylpromazine maleate) is a phenothiazine derivative that occurs as an odorless, bitter-tasting, yellow powder. One gram is soluble in 27 mL of water, 13 mL of alcohol, or 3 mL of chloroform. The injection is a clear, pale yellow to yellow solution.

Acepromazine maleate may also be known as ACE, *Aceproject®*, *Aceprotabs®*, acetylpromazine maleate, *Acevet®*, ACP, *Atravet®*, *Notensil®*, *PromAce®*, and *Plegicil®*.

Storage/Stability

Store tablets and injection protected from light at 20°C to 25°C (68°F-77°F), with excursions permitted between 15°C and 30°C (59°F-86°F). Tablets should be stored in tight containers. There is no limit to the number of vial punctures throughout the full expiry period.[1]

Compatibility/Compounding Considerations

Compatibility is dependent on factors such as pH, concentration, temperature, and diluent used; specialized references or a hospital pharmacist should be consulted for more specific information.

A study evaluating the stability, sterility, pH, particulate formation, and efficacy of compounded ketamine, acepromazine, and xylazine (KAX) in laboratory rodents supported the finding that the drugs are stable and efficacious for at least 180 days after mixing if stored at room temperature in the dark.[76] When injectable acepromazine is mixed with ketamine and xylazine and diluted with 0.9% saline, drug potency dropped below 90% between 1 and 2 months when stored in syringes at room temperature but retained more than 90% potency for 3 months when stored in syringes under refrigeration.[77] **NOTE:** Admixtures with ketamine or other controlled substances must be stored according to DEA requirements.

Combinations of acepromazine mixed with atropine, buprenorphine, chloral hydrate, meperidine, and oxymorphone have been commonly used, but studies documenting their compatibility and stability were not located. Both glycopyrrolate and diazepam have been reported to be physically **incompatible** with phenothiazines; however, glycopyrrolate has been demonstrated to be **compatible** with promazine HCl for injection.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

The Association of Racing Commissioners International (ARCI) has designated this drug as a class 3 substance. Use of this drug may not be allowed in certain animal competitions. Check rules and regulations before entering in a competition while this medication is being administered. Contact local racing authorities for further guidance. See ***Appendix*** for more information.

Acepromazine Maleate for Injection: 10 mg/mL for injection in 50 mL vials; *PromAce®*, generic; (Rx). FDA-approved forms available for use in dogs, cats, and horses not intended for food. Requires dilution or small syringes for safe and accurate dosing in small animals.

Acepromazine Maleate Tablets: 10 mg and 25 mg in bottles of 100 and 500 tablets; *PromAce®*, generic; (Rx)

In other countries, acepromazine is formulated in oral gels and powders and in varying strengths of injectable solutions (eg, 2 mg/mL, 25 mg/mL).

When used in an extra-label manner in food animals, it is recommended to contact Food Animal Residue Avoidance Databank (FARAD; see ***Appendix***) for further guidance.

HUMAN-LABELED PRODUCTS: NONE

References

For the complete list of references, see **wiley.com/go/budde/plumb**

Acetaminophen

APAP, Paracetamol

(ah-seet-a-***min***-a-fen) *Tylenol®*

Analgesic, Antipyretic

Prescriber Highlights

- ► **Contraindicated in cats and ferrets at any dosage**
- ► At recommended dosages, not overly toxic to dogs, rodents, or rabbits. Dogs are more susceptible than humans to red blood cell toxicity, so dose carefully.
- ► Often used in combined dosage forms with codeine, tramadol, or hydrocodone

Uses/Indications

Acetaminophen is used as an oral analgesic or antipyretic in dogs, horses, and small mammals. It may be particularly beneficial for the treatment of chronic pain conditions in dogs for which other analgesics (eg, NSAIDS, opioids) should not be used. In a clinical trial, acetaminophen was as effective as meloxicam and carprofen for postsurgical analgesia in bitches undergoing elective ovariohysterectomy.[1] For moderate pain, acetaminophen may be used in combination products containing codeine, hydrocodone, or tramadol. See the ***Codeine***, ***Tramadol***, and ***Hydrocodone Combinations*** monographs for more information on the use of acetaminophen combination preparations.

Acetaminophen has also been used for research purposes to measure gastric emptying in a variety of large animal species.[2–5]

Pharmacology/Actions

Acetaminophen's exact mechanisms of action are not completely un-

derstood. It produces analgesia and antipyresis via inhibition of cyclooxygenase and peroxidase sites on prostaglandin H_2 synthetase.[6] In addition, serotonergic activity may contribute to the drug's analgesic effect.[7] Unlike aspirin, acetaminophen does not possess significant anti-inflammatory activity or inhibit platelet function when given at clinically recommended dosages.

Pharmacokinetics

In dogs, acetaminophen oral bioavailability is 45%. Peak concentrations occur 20 to 50 minutes after oral dosing. Protein binding is ≈25%, and volume of distribution is 0.9 L/kg. Clearance is 1.5 to 2 L/kg/hour. Elimination half-life is ≈1 to 4 hours and appears to vary by breed.[8–13] Maximum plasma concentration, time at maximum concentration, and bioavailability are not affected by feeding in dogs.[14] In a study of hospitalized dogs receiving acetaminophen orally or rectally, rectal absorption was only 30% that of oral administration, and the drug did not reach concentrations associated with efficacy.[12]

In horses, peak concentration is reached ≈60 to 80 minutes after oral administration. Bioavailability is 91%. Volume of distribution is 0.82 to 2.7 L/kg and protein binding is 49%. Clearance is ≈0.25 L/kg/hour and elimination half-life is ≈2 to 4 hours.[11,15–17]

Acetaminophen was found to be stable in rumen fluid from cattle[18] and goats.[5] Oral bioavailability in cattle was 70%, peak concentration was reached after 1.4 hours, and elimination half-life was 2.4 hours.[18] In goats, oral bioavailability (16%) appeared to be limited, not by ruminal activity, but by first-pass metabolism.[5] Volume of distribution was 1.4 L/kg, and clearance was 53 mL/kg/minute.[19]

Similar bioavailability (42% to 75%) and half-lives (0.6 to 1.2 hours) were observed in a multi-species study that included pigs, turkeys, and chickens.[11]

Contraindications/Precautions/Warnings

Acetaminophen is contraindicated in cats at any dosage. Severe methemoglobinemia, hematuria, and icterus can be seen. Cats are deficient in glucuronyl transferases and are therefore unable to sufficiently glucuronidate acetaminophen; this leads to formation of active toxic metabolites (eg, free oxygen radicals) that cause oxidative injury and results in methemoglobinemia and formation of Heinz bodies in red blood cells. Acetaminophen should not be used in ferrets,[20] as in vitro studies indicate they may be as sensitive to acetaminophen as cats. At this time, acetaminophen should also not be used in sugar gliders or hedgehogs, as its safety has not been determined.

Dogs do not metabolize acetaminophen as well as humans do and its use must be judicious. Although dogs are not as sensitive as cats to acetaminophen, they may still be susceptible to methemoglobinemia when acetaminophen is prescribed at high dosages. Anecdotally, some dogs may be idiosyncratically sensitive to acetaminophen and some dogs may develop hepatotoxicity if acetaminophen is used chronically at therapeutic doses.[21]

Adverse Effects

At suggested dosages in dogs, there is potential for adverse renal, hepatic, GI, and hematologic effects. Higher dosages (3 times recommended) can cause keratoconjunctivitis sicca. In horses given acetaminophen for 14 days, increased total bilirubin and reduced sorbitol dehydrogenase activity were noted, and evidence of mild portal inflammation was noted on liver biopsies.[15]

Reproductive/Nursing Safety

Acetaminophen crosses the placenta.[22] Absolute reproductive safety has not been established; however, acetaminophen is considered relatively safe for occasional use in pregnancy.[23–25] In laboratory animals given acetaminophen at doses 0.85 to 1.2 times the maximum human dose (MHD, 4 g/day), reduced fetal weight and skeletal ossification, and focal renal and hepatic necrosis were observed.[26] Abnormal sperm and reduced testicular weight were noted in animals given 1.2 times MHD.[26]

Acetaminophen is excreted in milk in low concentrations with reported milk:plasma ratios of 0.91 to 1.42 at 1 and 12 hours, respectively; it is considered acceptable to administer to pregnant women.[27] In nursing human infants, no adverse effects have been reported.

Because safety has not been established in animals, this drug should only be used when the maternal benefits outweigh the potential risks to offspring.

Overdose/Acute Toxicity

Cats are highly susceptible to methemoglobinemia development because of their inability to glucuronidate acetaminophen, and there is no dose for cats that is considered safe. In the first few hours following ingestion, cats may present with swelling of the face and limbs. Doses of 40 mg/kg can cause methemoglobinemia, although some cats have been reported to develop it at 10 mg/kg. Because cats can develop methemoglobinemia rapidly after ingestion of acetaminophen, do not delay N-acetylcysteine treatment, and preferably give the first dose IV. See ***N-Acetylcysteine***. Clinical signs associated with methemoglobinemia include respiratory distress, cyanosis, depression, hypothermia, weakness, edema, and death. Hepatotoxicity occurs at higher doses; most cats are presented with methemoglobinemia signs before signs of hepatotoxicity develop.[28]

In dogs, hepatotoxicity generally occurs at doses greater than 75 – 100 mg/kg,[29,30] and clinical signs (eg, icterus, vomiting, anorexia, abdominal pain; coagulopathy, hypoglycemia, hepatic encephalopathy in severe cases) usually develop within 24 to 48 hours after ingestion. Many authors advise intervention with doses greater than 50 mg/kg. Methemoglobinemia generally occurs with doses greater than 200 mg/kg with clinical signs similar to those seen in cats. Signs typically develop 1 to 4 hours postexposure and persist for 12 to 48 hours. If the patient is left untreated, death can occur between 18 to 36 hours postexposure. Keratoconjunctivitis sicca can be seen with doses greater than 30 mg/kg, with clinical signs first seen 48 to 72 hours after exposure.[28]

For overdoses in dogs or cats, standard GI decontamination techniques with supportive care should be administered when applicable. Further treatment with N-acetylcysteine, *S*-adenosyl-methionine (SAMe), oxygen, and blood transfusions may be warranted.[29,31–34]

For patients that have experienced or are suspected to have experienced an overdose, consultation with a 24-hour poison consultation center specializing in providing veterinary-specific information is recommended. For general information related to overdose and toxin exposures, as well as contact information for poison control centers, refer to ***Appendix***.

Drug Interactions

The following drug interactions with acetaminophen have either been reported or are theoretical in humans or animals and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Anesthetics, Local** (eg, **bupivacaine, lidocaine, mepivacaine, ropivacaine**): Concurrent use may increase the risk for methemoglobinemia.
- **Barbiturates** (eg, **phenobarbital, primidone**): Increased conversion of acetaminophen to hepatotoxic metabolites; potentially increased risk for hepatotoxicity
- **Cholestyramine**: May reduce oral acetaminophen absorption; administer separately
- **Chloramphenicol:** Increased acetaminophen concentration noted in humans; veterinary significance is unclear.
- **Dipyrone:** Combined used may increase risk for hepatocellular injury.

- **Doxorubicin**: May deplete hepatic glutathione, leading to increased hepatic toxicity
- **Fenbendazole**: May increase the risk for hepatotoxicity (study done in mice)[35]
- **Isoniazid**: Increased conversion of acetaminophen to hepatotoxic metabolites with possible increased risk for hepatotoxicity
- **Leflunomide**: May increase the risk for hepatotoxicity
- **Metoclopramide:** May increase acetaminophen absorption
- **Metyrapone**: May reduce acetaminophen conjugation, potentially increasing formation of toxic acetaminophen metabolites
- **Penicillin G Benzathine and/or Procaine**: Concurrent use of the benzathine and/or procaine penicillin G salts may increase risk for methemoglobinemia.
- **Phenothiazines** (eg, **acepromazine**): Possible increased risk for hypothermia
- **Probenecid**: May increase acetaminophen concentration and alter its metabolism, potentially increasing formation of toxic acetaminophen metabolites
- **Propylene Glycol**: Foods containing propylene glycol (often found in wet cat foods) may increase the severity of acetaminophen-induced methemoglobinemia or Heinz body formation.
- **Rifampin**: May increase the risk for hepatotoxicity
- **Verdinexor**: Increases of serum concentration of either drug are possible due to competitive inhibition of glutathione S-transferase. Avoid combination if possible or monitor closely for adverse effects of each drug if combination cannot be avoided.
- **Warfarin**: Although acetaminophen is relatively safe to use, large doses may potentiate anticoagulant effects.

Laboratory Considerations

- False positive results may occur for urinary **5-hydroxyindoleacetic acid** (serotonin metabolite).

Dosages

NOTE: For dosages of acetaminophen combination products (with codeine or hydrocodone), refer to the individual ***Codeine*** and ***Hydrocodone Combinations*** monographs, respectively.

DOGS:

Analgesic or antipyretic (extra-label): 10 – 15 mg/kg PO or rectally every 8 hours; if using long-term (ie, more than 5 days), consider giving every 12 hours at the lower end of dosing range.

HORSES:

Analgesic or antipyretic (extra-label): 20 mg/kg PO once as single dose, or given twice daily[36,37]

RABBITS/RODENTS/SMALL MAMMALS:

Analgesic (extra-label): Using Children's *Tylenol®*, 1 – 2 mg acetaminophen/mL of drinking water. Effective for controlling mild to moderate pain[38–41]

Monitoring

- When used at recommended doses for pain control in otherwise healthy patients, little monitoring should be necessary. However, with chronic therapy, baseline and periodic liver, renal, and hematologic monitoring may be warranted, particularly when clinical signs occur.

Client Information

- Must **NEVER** be used in **cats**. Do **NOT** use in ferrets.
- Watch for side effects and contact your veterinarian if you see any of the following: dog stops eating, whites of the eyes become yellowish, continued vomiting or diarrhea, or blood seen in vomit or stool.
- Do **NOT** give more than your veterinarian prescribes. Unless your veterinarian instructs, do **NOT** give with other pain or fever medicine.
- Keep out of reach of children.

Chemistry/Synonyms

A synthetic nonopioid analgesic, acetaminophen (also known as paracetamol) occurs as a crystalline white powder with a slightly bitter taste. It is soluble in boiling water and freely soluble in alcohol. Acetaminophen is known in the UK as paracetamol.

Acetaminophen may also be known as paracetamol, *N*-acetyl-*p*-aminophenol, MAPAP or APAP; many trade names are available, *Tylenol®* is one common name.

Storage/Stability

Acetaminophen products should be stored at temperatures less than 40°C (104°F). Do not freeze the oral solution or suspension.

Compatibility/Compounding Considerations

Nonextended-release tablets may be split or crushed and mixed with food immediately prior to administration.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: NONE

The Association of Racing Commissioners International (ARCI) has designated this drug as a class 4 substance. See ***Appendix*** for more information. Use of this drug may not be allowed in certain animal competitions. Check rules and regulations before entering in a competition while this medication is being administered. Contact local racing authorities for further guidance.

HUMAN-LABELED PRODUCTS:

There are many different trade names and products of acetaminophen available commercially. The most commonly known trade name is *Tylenol®*. Acetaminophen is available in 160 mg, 325 mg, and 500 mg tablets, capsules, or caplets; 80 mg chewable tablets; 650 mg extended-release tablets; 32 mg/mL oral liquids, and 60 mg, 80 mg, 120 mg, 125 mg, 250 mg, 325 mg, and 650 mg rectal suppositories. Combinations with other analgesics (aspirin, codeine phosphate, hydrocodone, tramadol, or oxycodone) or antihistamines (diphenhydramine) are also available.

References

For the complete list of references, see **wiley.com/go/budde/plumb**

Acetazolamide

Acetazolamide Sodium

(a-set-a-***zole***-a-mide) *Diamox®*

Carbonic Anhydrase Inhibitor Diuretic; Antiglaucoma Agent

Prescriber Highlights

- ► May be used to treat metabolic alkalosis or glaucoma in small animals and hyperkalemic periodic paralysis (HYPP) in horses
- ► Contraindicated in patients with significant hepatic, renal, pulmonary, or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis, or electrolyte imbalance
- ► Give oral doses with food if GI upset occurs.
- ► Electrolytes and acid–base status should be monitored with chronic or high-dose therapy.
- ► Monitor with tonometry if using for glaucoma.

Uses/Indications

Acetazolamide has been used principally in veterinary medicine for its diuretic action and its effects on aqueous humor production in the treatment of metabolic alkalosis and glaucoma, respectively. This drug may be useful as an adjunctive treatment for increased CSF pressures associated with syringomyelia in dogs[1]; however, acetazolamide was ineffective in reducing clinical signs or the ventricle:brain

ratio in dogs with idiopathic communicating hydrocephalus.[2]

In horses, acetazolamide is used as a preventive and/or treatment for HYPP.

In humans, the drug has been used as adjunctive therapy for treatment of epilepsy and acute high-altitude sickness.

Pharmacology/Actions

Carbonic anhydrase inhibitors (CAIs) act via a noncompetitive, reversible inhibition of the enzyme carbonic anhydrase. Inhibition reduces the formation of hydrogen and bicarbonate ions from carbonic acid, which reduces the availability of these ions for active transport into body secretions.

Within the eye, the pharmacologic effect of CAIs is decreased formation of aqueous humor, which reduces intraocular pressure (IOP). Within the kidney, the pharmacologic effect of CAIs is increased renal tubular secretion of sodium and potassium and, to a greater extent, bicarbonate, leading to increased urine alkalinity and volume. Acetazolamide has some anticonvulsant activity, which is independent of its diuretic effects. This mechanism is not fully understood but may be caused by an effect on carbonic anhydrase in the brain or induction of metabolic acidosis.

In a study comparing the effects of acetazolamide and methazolamide in anesthetized cats, methazolamide did not reduce the hypoxic ventilatory response, but acetazolamide did. The study authors believe this response was not a result of carbonic anhydrase inhibition but instead was caused by acetazolamide's effects on carotid bodies or type I cells.[3]

Pharmacokinetics

One report states that in small animal species given acetazolamide 22 mg/kg (2 to 5 times the standard dosage), the onset of action for reduction of IOP is 30 minutes, maximal effects occur after 2 to 4 hours, and duration of action is ≈4 to 6 hours.[4]

In horses, IV administration of acetazolamide results in a high mean clearance rate (4.5 mL/kg/min) and a short mean residence time (1.71 hours). Immediate-release formulations show a low oral bioavailability (25%) with maximum concentrations of 1.9 µg/mL.[5]

In humans, the drug is well absorbed after oral administration, with peak concentrations occurring within 1 to 3 hours. The drug is distributed throughout the body, and the highest concentrations are found in the kidneys, plasma, and erythrocytes. Within 24 hours of oral tablet administration, an average of 90% of the drug is excreted unchanged into the urine by tubular secretion and passive reabsorption processes.

Contraindications/Precautions/Warnings

Carbonic anhydrase inhibitors (CAIs) are contraindicated in patients hypersensitive to them and in patients with significant hepatic disease (may precipitate hepatic coma), renal or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis, or other electrolyte imbalances. This class of drugs should not be used in patients with severe pulmonary obstruction that are unable to increase alveolar ventilation.

Acetazolamide should be used with caution in patients with severe respiratory acidosis or in those with pre-existing hematologic abnormalities. Chronic, high-dose administration may lead to decreased exercise capacity, hypercapnia, and respiratory acidosis in healthy horses during exercise.[6]

Although acetazolamide is a sulfonamide, cross-reactivity with antibacterial sulfonamides or furosemide does not appear to occur.[7] Do not confuse acetaZOLAMIDE with acetoHEXAMIDE or acetaMINOPHEN.

Adverse Effects

Potential adverse effects include GI disturbances (eg, nausea, vomiting, diarrhea, anorexia), CNS effects (eg, sedation, depression, weakness, excitement, paresthesias), hematologic effects (eg, bone marrow depression), renal effects (eg, crystalluria, dysuria, renal colic, polyuria), hypokalemia, hyperchloremia, hyperglycemia, hyponatremia, hyperuricemia, hepatic insufficiency, dermatologic effects (eg, rash), and hypersensitivity reactions, which includes Stevens-Johnson syndrome and toxic epidermal necrolysis. Acidosis occurred after IV administration of high-dose acetazolamide in dogs, and 3 dogs displayed mild tremors that resolved within 1 hour after administration.[8]

At the dosages used for HYPP in horses, adverse effects are reportedly uncommon.[9]

Reproductive/Nursing Safety

Acetazolamide crosses the placenta in unknown quantities. Acetazolamide has caused limb defects in laboratory animals and reduced fetal weight and incisor development in rats.[10] No effects on fertility were noted in rats. Fetal toxicity has been noted when the drug has been used in pregnant humans.

Acetazolamide is excreted in milk. Because safety has not been established in animals, this drug should only be used when the maternal benefits outweigh the potential risks to offspring. If unavoidable, use milk replacer instead of allowing offspring to nurse.

Overdose/Acute Toxicity

Information regarding overdose with this drug is not available. Monitor serum electrolytes, venous blood gases (including pH), hydration status, and CNS status during an acute overdose; treat clinical signs and provide supportive treatment. Acetazolamide is dialyzable.

For patients that have experienced or are suspected to have experienced an overdose, consultation with a 24-hour poison consultation center specializing in providing veterinary-specific information is recommended. For general information related to overdose and toxin exposures, as well as contact information for poison control centers, refer to ***Appendix***.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving acetazolamide and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Cyclosporine**: Acetazolamide may increase concentrations.
- **Digoxin**: As acetazolamide may cause hypokalemia, there is an increased risk for digoxin toxicity.
- **Drugs Affecting Potassium** (eg, **amphotericin B, corticosteroids** [eg, **dexamethasone, prednis(ol)one], corticotropin, or other diuretics**): Concomitant use may exacerbate potassium depletion.
- **Folic Acid Antagonists** (eg, **pyrimethamine, sulfadiazine, sulfadimethoxine, trimethoprim**): May augment folic acid antagonism
- **Insulin**: Rarely, CAIs interfere with the hypoglycemic effects of insulin.
- **Methenamine Compounds**: Acetazolamide may negate methenamine effects in the urine.
- **Methotrexate:** May augment folic acid antagonism
- **Phenobarbital**: Acetazolamide-induced alkaline urine may increase urinary excretion and compromise efficacy.
- **Primidone**: May reduce primidone absorption and serum concentration
- **Procainamide**: Acetazolamide-induced alkaline urine may decrease urinary excretion of procainamide; procainamide toxicity is possible.
- **Quinidine**: Acetazolamide-induced alkaline urine may decrease urinary excretion of quinidine; quinidine toxicity is possible.