ACETAMINOPHEN

PHARMACOLOGY
Acetaminophen produces analgesia and antipyresis via mechanisms similar to the salicylates (inhibition of cyclooxygenase). Unlike aspirin, it does not possess significant antiinflammatory activity.

USES/INDICATIONS
Acetaminophen is occasionally used as an oral analgesic in dogs. In conditions of more severe pain, it may be used in combination with oral codeine phosphate.

PHARMACOKINETICS
Specific pharmacokinetic information in domestic animals was not located. In humans, acetaminophen is rapidly and nearly completely absorbed from the gut and is rapidly distributed into most tissues. Approximately 25% is plasma protein bound. Dogs apparently exhibit dose dependent metabolism (saturable).

CONTRAINDICATIONS/RECLUSIONS/REPRODUCTIVE SAFETY
Acetaminophen is contraindicated in cats at any dosage. Severe methemoglobinemia, hematuria, and icterus can be seen. Cats apparently are unable to significantly glucuronidate acetaminophen leading to toxic metabolites being formed and resultant toxicity. Dogs also do not metabolize acetaminophen as well as humans and its use must be judicious. In dogs, it is generally not recommended to use acetaminophen during the immediate post-operative phase (first 24 hours) due to an increased risk of hepatotoxicity developing.

Absolute reproductive safety has not been established, but acetaminophen is apparently relatively safe for occasional use in pregnancy (no documented problems in humans). Animal data not located.

ADVERSE EFFECTS/WARNINGS
Because acetaminophen is not routinely used in veterinary medicine, experience on its adverse effect profile is limited. At suggested dosages in dogs, there is some potential for renal, hepatic, GI and hematologic effects occurring.

OVERDOSEAGE
Because of the potentially severe toxicity associated with acetaminophen, consultation with an animal poison center is recommended (see appendix). For overdosage in dogs or cats, standard gut emptying techniques and supportive care should be administered when applicable. Further treatment with acetylcysteine may be warranted (see acetylcysteine monograph for more information).
**Drug Interactions**
Large doses may potentiate the effects of coumarin or indandione anticoagulants. Doxorubicin may deplete hepatic glutathione, thereby leading to increased hepatic toxicity. Acetaminophen is not recommended to be used for post-operative analgesia in animals who received halothane anesthesia. Chronic use of acetaminophen in combination with other analgesics may lead to renal pathologies.

**Laboratory Considerations**
False positive results may occur for urinary 5-hydroxyindoleacetic acid.

**Doses**

**Dogs**
As an analgesic:
- a) 15 mg/kg PO q8h (Dodman 1992); (McLaughlin 2000)
- b) 10 mg/kg PO q12h (Kelly 1995)
- b) In the treatment of degenerative myelopathy (in German Shepherds): 5 mg/kg PO (not to exceed 20 mg/kg per day) (Clemmons 1991)

In combination with codeine as an analgesic:
- a) Using a 60 mg codeine and 300 mg acetaminophen fixed-dose tablet (e.g., Tylenol® #4), give 1 - 2 mg/kg (of the codeine) PO q6-8h. (Hansen 1994), (Hardie 2000)

**Rabbits/Rodents/Pocket Pets**
As an analgesic:
- b) **Rabbits**: Using acetaminophen and codeine elixir: 1 ml in 10-20 ml of drinking water (add dextrose to enhance palatability) (Ivey and Morrisey 2000)
- c) **Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas**: 1 - 2 mg/ml in drinking water (Adamcak and Otten 2000)

**Monitoring Parameters**
When used at recommended doses in otherwise healthy dogs for pain control, little monitoring should be necessary. However, with chronic therapy occasional liver, renal and hematologic monitoring may be warranted, particularly when symptoms occur.

**Client Information**
Follow directions carefully; do not exceed dosage or increase dosing frequency. Do not for any reasons administer to cats. Keep out of reach of children.

**Human-Approved Products**
There are many different trade names and products of acetaminophen available. The most commonly known trade name is Tylenol®. Acetaminophen is commonly available in 160 mg, 325 mg, 500 mg tablets, 650 mg tablets; 80 mg chewable tablets; 160 mg, 500 mg, 650 mg (extended release) caplets; 500 mg gelcaps; 325 mg, 500 mg, capsules, 80 mg & 160 mg sprinkle capsules; 80 mg/0.8 ml, 80 mg/2.5 ml, 80 mg/5 ml, 120 mg/5 ml, 160 mg/5 ml elixir; 160 mg/5 ml, 500 mg/15 ml, 80 mg/1.66 ml, & 100 mg/ml oral solutions and suspensions; 80 mg, 120 mg, 125 mg 300 mg, 325 mg & 650 mg suppositories. Combinations with other analgesics (aspirin, codeine phosphate, oxycodone or propoxyphene) are also available.

See the codeine monograph for more information on the use of acetaminophen-codeine combination preparations.
**Butorphanol Tartrate**

**Prescriber Highlights**

- Partial opiate agonist/antagonist used in a variety of species as an analgesic, premed, antitussive, or antiemetic.
- Contraindicated or caution in pts. w/ liver disease, hypothyroidism, renal insufficiency, Addison’s, head trauma, increased CSF pressure or other CNS dysfunction (e.g., coma) and in geriatric or severely debilitated patients.
- Potential adverse effects in dogs/cats: sedation, ataxia, anorexia or diarrhea (rarely).
- Horses (at usual doses) may include a transient ataxia and sedation, but CNS excitement possible.
- Controlled substance (C-IV)

**Chemistry**

A synthetic opiate partial agonist, butorphanol tartrate is related structurally to morphine but exhibits pharmacologic actions similar to other partial agonists such as pentazocine or nalbuphine. The compound occurs as a white, crystalline powder that is sparingly soluble in water and insoluble in alcohol. It has a bitter taste and a $pK_a$ of 8.6. The commercial injection has a pH of 3-5.5. One mg of the tartrate is equivalent to 0.68 mg of butorphanol base.

**Storage/Stability/Compatibility**

The injectable product should be stored out of bright light and at room temperature; avoid freezing.

The injectable product is reported to be **compatible** with the following IV fluids and drugs: acepromazine, atropine sulfate, chlorpromazine, diphenhydramine HCl, droperidol, fentanyl citrate, hydroxyzine HCl, meperidine, morphine sulfate, pentazocine lactate, perphenazine, prochlorperazine, promethazine HCl, scopolamine HBr, and xylazine.

The drug is reportedly **incompatible** with the following agents: dimenhydrinate, and pentobarbital sodium.

**Pharmacology**

Butorphanol is considered to be, on a weight basis, 4-7 times as potent an analgesic as morphine, 15-30 times as pentazocine, and 30-50 times as meperidine. Its agonist activity is thought to be exerted primarily at the *kappa* and *sigma* receptors and the analgesic actions at sites in the limbic system (subcortical level and spinal levels).

The antagonist potency of butorphanol is considered to be approximately 30 times that of pentazocine and 1/40th that of naloxone and will antagonize the effect of true agonists (e.g., morphine, meperidine, oxymorphone).

Besides the analgesic qualities of butorphanol, it possesses significant antitussive activity. In dogs, butorphanol has been shown to elevate CNS respiratory center threshold to CO$_2$, but unlike opiate agonists, not depress respiratory center sensitivity. Butorphanol, unlike morphine, apparently does not cause histamine release in dogs. CNS depression may occur in dogs, while CNS excitation has been noted (usually at high doses) in horses and dogs.

Although possessing less cardiovascular effects than the classical opiate agonists, butorphanol can cause a decrease in cardiac rate secondary to increased parasympathetic tone and mild decreases in arterial blood pressures.

The risk of causing physical dependence seems to be minimal when butorphanol is used in veterinary patients.

**Pharmacokinetics**

Butorphanol is absorbed completely in the gut when administered orally, but because of a high first-pass effect only about 1/6$^{th}$ of the administered dose reaches the systemic circulation. The drug has also been shown to be completely absorbed following IM administration.
Butorphanol is well distributed, with highest levels (of the parent compound and metabolites) found in the liver, kidneys, and intestine. Concentrations in the lungs, endocrine tissues, spleen, heart, fat tissue and blood cells are also higher than those found in the plasma. Approximately 80% of the drug is bound to plasma proteins (human data). Butorphanol will cross the placenta and neonatal plasma levels have been roughly equivalent to maternal levels. The drug is also distributed into maternal milk.

Butorphanol is metabolized in the liver, primarily by hydroxylation. Other methods of metabolism include N-dealkylation and conjugation. The metabolites of butorphanol do not exhibit any analgesic activity. These metabolites and the parent compound are mainly excreted into the urine (only 5% is excreted unchanged), but 11-14% of a dose is excreted into the bile and eliminated with the feces.

Following IV doses in horses, the onset of action is approximately 3 minutes with a peak analgesic effect at 15-30 minutes. The duration of action in horses may be up to 4 hours after a single dose.

**Uses/Indications**

Approved indication for dogs is "for the relief of chronic non-productive cough associated with tracheobronchitis, tracheitis, tonsillitis, laryngitis and pharyngitis originating from inflammatory conditions of the upper respiratory tract" (Package Insert; Torbutrol® - Fort Dodge). It is also used in practice in both dogs and cats as a preanesthetic medication, analgesic, and as an antiemetic prior to cisplatin treatment (although not very effective in cats for this indication).

The approved indication for horses is "for the relief of pain associated with colic in adult horses and yearlings" (Package Insert; Torbugesic® - Fort Dodge). It has also been used clinically as an analgesic in cattle, although published data is apparently lacking.

**Contraindications/Precautions**

All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison’s), and in geriatric or severely debilitated patients.

Like other opiates, butorphanol must be used with extreme caution in patients with head trauma, increased CSF pressure or other CNS dysfunction (e.g., coma).

The manufacturer states that butorphanol "should not be used in dogs with a history of liver disease", and because of its effects on suppressing cough, "it should not be used in conditions of the lower respiratory tract associated with copious mucous production." The drug should be used cautiously in dogs with heartworm disease as safety for butorphanol has not been established in these cases.

Although no controlled studies have been performed in domestic animals or humans, the drug has exhibited no evidence of teratogenicity or of causing impaired fertility in laboratory animals. The manufacturer, however, does not recommend its use in pregnant bitches, foals, weanlings (equine), and breeding horses.

The drug is contraindicated in patients having known hypersensitivity to it.

**Adverse Effects/Warnings**

Adverse effects reported in dogs/cats include sedation (occasionally), ataxia, anorexia or diarrhea (rarely).

Adverse effects seen in horses (at usual doses) may include a transient ataxia and sedation, but excitement has been noted as well (see below). Although reported to have minimal effects on the GI, butorphanol has the potential to decrease intestinal motility. Horses may exhibit CNS excitement (tossing and jerking of head, increased ambulation, augmented avoidance response to auditory stimuli) if given high doses (0.2 mg/kg) IV rapidly. Very high doses IV (1 - 2 mg/kg) may lead to the development of nystagmus, salivation, seizures, hyperthermia and decreased GI motility. These effects are considered to be transitory in nature.

**Overdosage**

Acute life-threatening overdoses with butorphanol should be unlikely. The LD₉₀ in dogs is reportedly 50 mg/kg. However, because butorphanol injection is available in two dosage strengths (0.5 mg/ml and 10 mg/ml) for veterinary use, the possibility exists that inadvertent overdoses may occur in small animals.
It has been suggested that animals exhibiting symptoms of overdose (CNS effects, cardiovascular changes, and respiratory depression) be treated immediately with intravenous naloxone. Additional supportive measures (e.g., fluids, \(O_2\), vasopressor agents, & mechanical ventilation) may be required. Should seizures occur and persist, diazepam may be used for control.

**Drug Interactions**

Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with butorphanol, dosage may need to be decreased.

Pancuronium if used with butorphanol may cause increased conjunctival changes.

**Doses**

Note: All doses are expressed in mg/kg of the base activity. If using the human product (Stadol\(^\text{®}\)), 1 mg of tartrate salt = 0.68 mg base.

**Dogs**

As an antitussive:
- a) 0.055 - 0.11 mg/kg SC q6-12h; treatment should not normally be required for longer than 7 days; or 0.55 mg/kg PO q6-12h; may increase dose to 1.1 mg/kg PO q6-12h (The oral doses correspond to one 5 mg tablet per 20 lbs. and 10 lbs. of body weight, respectively); treatment should not normally be required for longer than 7 days. (Package Insert; Torbutrol\(^\text{®}\); - Fort Dodge)
- b) 0.05 - 1 mg/kg PO q6-12h; goal is to suppress coughing without causing excessive sedation (Johnson 2000)
- c) 0.5 - 1.2 mg/kg PO twice to 4 times a day (Johnson 2000)

As an analgesic:
- a) 0.1 - 1 mg/kg IM, IV or SC q1-3h (Hendrix and Hansen 2000)
- b) 0.2 - 0.4 mg/kg SC, IM or IV (use lower dose if given IV); Efficacy is 1-2 hours for moderate pain and 2-4 hours for mild pain. May give orally at 0.4 mg/kg to the nearest quarter tablet 3 times a day (Mathews 1999)
- c) 0.5 - 1 mg/kg PO q6-8h (Hardie 2000)

As a preanesthetic:
- a) 0.05 mg/kg IV or 0.4 mg/kg SC, IM (Morgan 1988)
- b) 0.2 - 0.4 mg/kg IM (with acepromazine 0.02 - 0.04 mg/kg IM) (Reidesel)

As an anti-emetic prior to cisplatin treatment:
- a) 0.4 mg/kg IM 1/2 hour prior to cisplatin infusion. (Klausner and Bell 1988)

**Cats**

As an analgesic:
- a) 0.1 - 1 mg/kg IM, IV or SC q1-3h (Hendrix and Hansen 2000)
- b) 0.2 - 0.4 mg/kg SC, IM or IV (use lower dose if given IV); Efficacy is 1-2 hours for moderate pain and 2-4 hours for mild pain. May give orally at 0.4 mg/kg to the nearest quarter tablet 3 times a day (Mathews 1999)
- c) 0.5 - 1 mg/kg PO q6-8h (Hardie 2000)

As a preanesthetic:
- a) 0.2 - 0.4 mg/kg IM (with glycopyrrolate 0.01 mg/kg IM & ketamine 4 - 10 mg/kg IM) (Reidesel)
**Ferrets**

a) As a sedative/analgesic: Butorphanol alone 0.05 - 0.1 mg/kg IM, SC. Butorphanol/Xylazine: Butorphanol 0.2 mg/kg + Xylazine 2 mg/kg IM

For injectable anesthesia: Butorphanol 0.1 mg/kg, Ketamine 5 mg/kg, medetomidine 80 mcg/kg. Combine in one syringe and give IM. May need to supplement with isoflurane (0.5 - 1.5%) for abdominal surgery. (Finkler 1999)

b) Xylazine (2 mg/kg) plus butorphanol (0.2 mg/kg) IM; Telazol (1.5 mg/kg) plus xylazine (1.5 mg/kg) plus butorphanol (0.2 mg/kg) IM; may reverse xylazine with yohimbine (0.05 mg/kg IM) (Williams 2000)

c) As an analgesic: 0.05 - 0.5 mg/kg SC or IM q4h (Williams 2000)

**Rabbits/Rodents/Pocket Pets**

a) For chemical restraint in Rabbits: 0.1 - 0.5 mg/kg IV (Burke 1999); (Ivey and Morrisey 2000)

b) For postsurgical analgesia in Rabbits: 0.1 - 0.5 mg/kg IV or SC q2-4h; lower dosages may be more effective due to "ceiling effect" (Ivey and Morrisey 2000)

c) Rabbits: As an analgesic (post-operative pain): 0.4 mg/kg SC q4-6h

For surgical procedures (in combo with xylazine/ketamine): 0.1 mg/kg once IM or SC (Huerkamp 1995)

**Birds**

a) 3 - 4 mg/kg IM. True analgesic effects unknown in avian species, but has no detrimental respiratory or cardiovascular effects. Mild motor deficits may be observed. (Wheler 1993)

b) As analgesic: Psittacines: 2 - 4 mg/kg IM; frequent re-dosing every 2-4 hours is needed to maintain analgesia. If adverse effects are an issue (e.g., respiratory or cardiovascular depression), may reverse with naloxone (0.05 - 0.25 mg/kg IM or slow IV) (Clyde and Paul-Murphy 2000)

**Cattle**

As an analgesic for surgery in adult cattle:

a) 20 - 30 mg IV (jugular) (may wish to pretreat with 10 mg xylazine) (Powers 1985)

**Horses**

**Note: ARCI UCGFS Class 3 Drug**

As an analgesic:

a) 0.1 mg/kg IV q3-4h; not to exceed 48 hours (Package Insert; Torbugesic®; - Fort Dodge)

b) For moderate to marked abdominal pain: 0.01 - 0.02 mg/kg IV alone or in combination with xylazine (0.02 - 0.1 mg/kg IM) (Moore 1999)

c) 0.02 - 0.1 mg/kg IV; or 0.04 - 0.2 mg/kg IM q3-4h (combined with acepromazine or xylazine) (Orsini 1988)

As a preanesthetic, outpatient surgery, or chemical restraint:

a) 0.01 - 0.04 mg/kg IV (with xylazine 0.1 - 0.5 mg/kg IV) (Orsini 1988)

b) For field anesthesia: Sedate with xylazine (1 mg/kg IV; 2 mg/kg IM) given 5-10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either 1) Redose xylazine: up to half the original dose, 2) Add butorphanol (0.02-0.04 mg/kg IV). Butorphanol can be given with the original xylazine if you suspect that the horse will be difficult to tranquilize (e.g., high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5-10 minutes. 3) Diazepam (0.03 mg/kg IV). Mix the diazepam with the ketamine.
This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5-10 minutes. 4) Guaifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)

As an antitussive:
   a) 0.02 mg/kg IM bid-tid (Orsini 1988)

**Monitoring Parameters**

1) Analgesic &/or antitussive efficacy
2) Respiratory rate/depth
3) Appetite/bowel function
4) CNS effects

**Client Information**

Clients should report any significant changes in behavior, appetite, bowel or urinary function in their animals.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times**

Note: Butorphanol is a class IV controlled substance. The veterinary products (Torbutrol®, Torbugesic®) strengths are listed as base activity. The human product (Stadol®) strength is labeled as the tartrate salt.

**Veterinary-Approved Products**

Butorphanol Tartrate Injection; 0.5 mg/ml (activity as base) 10 ml vials; Torbutrol® (Fort-Dodge); (Rx) (C-IV) Approved for use in dogs.

Butorphanol Tartrate Injection; 2 mg/ml (as tartrate) in 10 ml vials. Torbugesic-SA® (Fort Dodge) (Rx) (CIV). Approved for use in cats.

Butorphanol Tartrate Injection; 10 mg/ml (activity as base) 50 ml vials; Torbugesic® (Fort-Dodge), Dolorex® (Intervet); (Rx)(CIV) Approved for use in horses not intended for food.

Butorphanol Tartrate Tablets (Veterinary); 1 mg, 5 mg, & 10 mg (activity as base) tablets; bottles of 100; Torbutrol® (Fort-Dodge); (Rx) (CIV) Approved for use in dogs.

**Human-Approved Products**

Butorphanol Tartrate Injection; 1 mg/ml (as tartrate salt; equivalent to 0.68 mg base) in 1 ml vials and 2 mg/ml (as tartrate salt) in 1, 2, & 10 ml vials; Stadol® (Mead Johnson); (Rx) (C-IV)

Butorphanol Nasal Spray: 10 mg/ml (2.5 ml metered dose) Stadol NS® (Mead Johnson) (Rx) (C-IV)
**Coprofen**

**Prescriber Highlights**
- NSAID used in dogs and other small animals
- Contraindicated in dogs w/ bleeding disorders (e.g., Von Willebrand's), history of serious reactions to it or other propionic-class NSAIDs
- Caution: in geriatric patients or those with preexisting chronic diseases (e.g., inflammatory bowel disease, renal or hepatic insufficiency)
- GI adverse effects are less likely, but can occur
- Rarely may cause hepatic failure; monitor liver enzymes
- Drug-drug, drug-lab interactions

**Chemistry**
A propionic acid derivative non-steroidal antiinflammatory agent, carprofen occurs as a white crystalline compound. It is practically insoluble in water and freely soluble in ethanol at room temperature. Carprofen has both an S enantiomer and R enantiomer. The commercial product contains a racemic mixture of both. The S (+) enantiomer has greater antiinflammatory potency than the R (-) form.

**Storage/Stability/Compatibility**
The commercially available caplets should be stored at room temperature (15-30°C).

**Pharmacology**
Like other NSAIDs, carprofen exhibits analgesic, anti-inflammatory, and antipyretic activity probably through its inhibition of cyclooxygenase, phospholipase A₂ and inhibition of prostaglandin synthesis.

**Uses/Indications**
Carprofen is indicated for the relief of pain and inflammation in dogs. It may also prove to be of benefit in other species as well, but data are scant to support its safe use at this time. In Europe, carprofen is reportedly registered for single dose use in cats, but there have been reported problems (e.g., vomiting) with cats receiving more than a single dose.

**Pharmacokinetics**
When administered orally to dogs, carprofen is approximately 90% bioavailable. Peak serum levels occur between 1-3 hours post dosing. The drug is highly bound to plasma proteins (99%) and has a low volume of distribution (0.12 - 0.22 l/kg). Carprofen is extensively metabolized in the liver primarily via glucuronidation and oxidative processes. About 70-80% of a dose is eliminated in the feces; 10-20% eliminated in the urine. Some enterohepatic recycling of the drug occurs. Elimination half-life of carprofen in the dog is approximately 13 - 18 hours with the S form having a longer half life than the R form. In horses, the half-life of carprofen is reportedly 22 hours.

**Contraindications/Precautions/Reproductive Safety**
Carprofen is contraindicated in dogs with bleeding disorders (e.g., Von Willebrand's), those that have had prior serious reactions to it or other propionic-class antiinflammatory agents. It should be used with caution in geriatric patients or those with preexisting chronic diseases (e.g., inflammatory bowel disease, renal or hepatic insufficiency).

**Adverse Effects/Warnings**
Although adverse effects appear to be uncommon with carprofen use in dogs, they can occur. Mild gastrointestinal effects are the most likely to appear, but serious effects (hepatocellular damage and/or renal disease; hematologic and serious gastrointestinal effects) have been reported. Geriatric dogs or dogs with chronic diseases (e.g., inflammatory bowel disease, renal or hepatic insufficiency) may be at greater risk for developing toxicity while taking this drug. Although not proven to be statistically significant, Labrador Retrievers have been associated with 1/3 of the initial cases associated with the reported hepatic syndrome. Before initiating therapy, pre-treatment patient evaluation and discussion with the owner regarding the potential risks versus benefits of therapy are strongly advised.
**OVERDOSAGE**
In dog toxicologic studies, repeated doses of up to 10X resulted in little adversity. Some dogs exhibited hypoalbuminemia, melena or slight increases in ALT. However, post-marketing surveillance suggests that there may be significant interpatient variability in response to acute or chronic overdoses.

**DRUG INTERACTIONS**
Note: Although the manufacturer does not list any specific drug interactions in the package insert, it does caution to avoid or closely monitor carprofen's use with other ulcerogenic drugs (e.g., corticosteroids or other NSAIDs).

In humans, there are many interactions possible with NSAIDs. Because clinical experience is limited in dogs, the following may or may not be clinically significant: Because carprofen is highly bound to plasma proteins (99%) it may displace other highly bound drugs. Increased serum levels and duration of actions of phenytoin, valproic acid, oral anticoagulants, other anti-inflammatory agents, salicylates, sulfonamides, and the sulfonylurea antidiabetic agents may occur.

When aspirin is used concurrently with carprofen, plasma levels of carprofen could decrease and an increased likelihood of GI adverse effects (blood loss) could occur. Concomitant administration of aspirin with carprofen cannot be recommended.

Probenecid may cause a significant increase in serum levels and half-life of carprofen.

Serious toxicity has occurred when NSAIDs have been used concomitantly with methotrexate; use together with extreme caution.

Carprofen may reduce the saluretic and diuretic effects of furosemide and increase serum levels of digoxin. Use with caution in patients with severe cardiac failure.

**LABORATORY INTERACTIONS**
In dogs, carprofen may lower Total T<sub>4</sub> and TSH levels in dogs, but apparently does not affect free concentrations of T<sub>4</sub>.

**DOSES**

**Dogs**
As an antiinflammatory/analgesic:
- a) 2.2 mg/kg PO twice daily; round dose to nearest half caplet increment (Package Insert; Rimadyl®-Pfizer)
- b) For surgical pain: 4 mg/kg IV initially once; 2.2 mg/kg PO, IV, SC or IM, repeat in 12 hours if needed.
- For chronic pain: 2.2 mg/kg PO q12h (Johnson 1996)
- c) 2 mg/kg PO q12h (Hardie 2000)

**Cats**
As an antiinflammatory/analgesic: Caution is advised, particularly with long term dosing.
- a) For surgical pain: 4 mg/kg IV initially once; 2.2 mg/kg PO, IV, SC or IM, repeat in 12 hours if needed.
- For chronic pain: 2.2 mg/kg PO q12h (Johnson 1996)
- b) 2 mg/kg PO q12h; limit to 2 days of therapy (Hardie 2000)

**Rabbits/Rodents/Pocket Pets**
- a) **Rabbits**: For chronic joint pain: 2.2 mg/kg PO q12h (Ivey and Morrisey 2000)
- b) **Rats**: 5 mg/kg SC or 5 - 10 mg/kg PO. **Chinchillas**: 4 mg/kg SC once daily (Adamcak and Otten 2000)

**Horses**
As an antiinflammatory/analgesic: 0.7 mg/kg IV, one time (Note: parenteral form not available in USA) (Clark and Clark 1999)
**Birds**

As an antiinflammatory/analgesic: 2 mg/kg PO q8-24 hours (Clyde and Paul-Murphy 2000)

**MONITORING PARAMETERS**

1) Baseline (especially in geriatric dogs or dogs with chronic diseases or those where prolonged treatment is likely): physical exam, CBC, Serum chemistry panel (including liver and renal function tests), UA. It is recommended to reassess the liver enzymes at one week of therapy. Should elevation occur, recommend discontinuing the drug. 2) Clinical efficacy 3) Signs of potential adverse reactions: inappetence, diarrhea, vomiting, melena, polyuria/polydipsia, anemia, jaundice, lethargy, behavior changes, ataxia or seizures 4) Chronic therapy: Consider repeating CBC, UA and serum chemistries on an ongoing basis

**CLIENT INFORMATION**

Although rare, serious adverse effects have been reported with the use of this drug. Clients should be informed of the risks associated with its use and be alerted to monitor for signs of potential adverse effects (see above). Should these signs present, clients should stop the drug immediately and contact their veterinarian.

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS**

**Veterinary Approved Products**

Carprofen 25 mg, 75 mg & 100 mg scored caplets or chewable tablets in bottles of 14, 60 or 180.; Rimadyl® Caplets & Rimadyl® Chewable Tablets (Pfizer); (Rx). Approved for use in dogs.

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**DIAZEPAM**

**PRESCRIBER HIGHLIGHTS**

- Benzodiazepine used for a variety of indications (anxiolytic, muscle relaxant, hypnotic, appetite stimulant, and anticonvulsant) in several species
- Contraindicated: Hypersensitivity to benzodiazepines, cats exposed to chlorpyrifos, significant liver disease (especially in cats)
- Caution: hepatic or renal disease, aggressive, debilitated or geriatric patients; patients in coma, shock or with significant respiratory depression
- Adverse effects: Sedation and ataxia most prevalent. Dogs: CNS excitement; cats: hepatic failure or behavior changes; horses: muscle fasciculations
- Inject slowly IV
- May be teratogenic
- Drug interactions
- Controlled substance (C-IV)

**CHEMISTRY**

A benzodiazepine, diazepam is a white to yellow, practically odorless crystalline powder with a melting point between 131°-135°C and pKₐ of 3.4. Diazepam is tasteless initially, but a bitter after-taste develops. One gram is soluble in 333 ml of water, 25 ml of alcohol, and it is sparingly soluble in propylene glycol. The pH of the commercially prepared injectable solution is adjusted with benzoic acid/sodium benzoate to 6.2-6.9. It consists of a 5 mg/ml solution with 40% propylene glycol, 10% ethanol, 5% sodium benzoate/benzoic acid buffer, and 1.5% benzyl alcohol as a preservative.

**STORAGE/Stability/Compatibility**

All diazepam products should be stored at room temperature (15°-30°C). The injection should be kept from freezing and protected from light. The oral dosage forms (tablets/capsules) should be stored in tight containers and protected from light.
Because diazepam may adsorb to plastic, it should not be stored drawn up into plastic syringes. The drug may also significantly adsorb to IV solution plastic (PVC) bags and to the infusion tubing. This adsorption appears to be dependent on several factors (temperature, concentration, flow rates, line length, etc.).

The manufacturers of injectable diazepam do not recommend the drug be mixed with any other medication or IV diluent. The drug has been successfully diluted to concentrations of 5 mg/50 ml or 5 mg/100 ml in normal saline, lactated Ringer's and D5W. Differing results have occurred with different manufacturer's products. Do not administer if a precipitate forms and does not clear.

**PHARMACOLOGY**

The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed by diazepam and other benzo diazepines thus producing the anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects seen. The exact mechanism of action is unknown, but postulated mechanisms include: antagonism of serotonin, increased release of and/or facilitation of gamma-aminobutyric acid (GABA) activity, and diminished release or turnover of acetylcholine in the CNS. Benzodiazepine specific receptors have been located in the mammalian brain, kidney, liver, lung, and heart. In all species studied, receptors are lacking in the white matter.

**USES/INDICATIONS**

Diazepam is used clinically for its anxiolytic, muscle relaxant, hypnotic, appetite stimulant, and anticonvulsant activities. Refer to the dosage section for those and other suggested indications and doses for each species.

**PHARMACOKINETICS**

Diazepam is rapidly absorbed following oral administration. Peak plasma levels occur within 30 minutes to 2 hours after oral dosing. The drug is slowly (slower than oral) and incompletely absorbed following IM administration.

Diazepam is highly lipid soluble and is widely distributed throughout the body. It readily crosses the blood-brain barrier and is fairly highly bound to plasma proteins. In the horse at a serum concentration of 75 ng/ml, 87% of the drug is bound to plasma proteins. In humans, this value has been reported to be 98-99%.

Diazepam is metabolized in the liver to several metabolites, including desmethyldiazepam (nordiazepam), temazepam, and oxazepam, all of which are pharmacologically active. These are eventually conjugated with glucuronide and eliminated primarily in the urine. Because of the active metabolites, serum values of diazepam are not useful in predicting efficacy. Serum half-lives (approximated) have been reported for diazepam and metabolites in dogs, cats, and horses:

<table>
<thead>
<tr>
<th></th>
<th>Dogs</th>
<th>Cats</th>
<th>Horses</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>2. 5 - 3.2 hrs</td>
<td>5. 5 hrs</td>
<td>7 - 22 hrs</td>
<td>20 - 50 hrs</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>3 hrs</td>
<td>21.3 hrs</td>
<td>30 - 200 hrs</td>
<td></td>
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</table>

**CONTRAINDICATIONS/PRECAUTIONS**

Slowly inject intravenously. This is particularly true when using a small vein for access or in small animals. Diazepam may cause significant thrombophlebitis. Too rapid of an injection of intravenous diazepam in small animals or neonates, may cause cardiotoxicity secondary to the propylene glycol in the formulation. Intra-carotid artery injections must be avoided.

Use cautiously in patients with hepatic or renal disease and in debilitated or geriatric patients. The drug should be administered to patients in coma, shock or with significant respiratory depression very cautiously. It is contraindicated in patients with known hypersensitivity to the drug. Diazepam should be used very cautiously, if at all, in aggressive patients as it may disinhibit the anxiety that may help prevent these animals from aggressive behavior. Benzodiazepines may impair the abilities of working animals. If administering the drug IV, be prepared to administer cardiovascular or respiratory support.
It is recommended not to use diazepam for seizure control in cats exposed to chlorpyrifos as organophosphate toxicity may be potentiated.

Diazepam has been implicated in causing congenital abnormalities in humans if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feeding, hyperbilirubinemia, hypotonia, etc. Withdrawal symptoms have occurred in infants whose mothers chronically took benzodiazepines during pregnancy. The veterinary significance of these effects is unclear, but the use of these agents during the first trimester of pregnancy should only occur when the benefits clearly outweigh the risks associated with their use. Benzodiazepines and their metabolites are distributed into milk and may cause CNS effects in nursing neonates.

**ADVERSE EFFECTS/WARNINGS**

In horses, diazepam may cause muscle fasciculations, weakness and ataxia at doses sufficient to cause sedation. Doses greater than 0.2 mg/kg may induce recumbency as a result of its muscle relaxant properties and general CNS depressant effects.

Cats may exhibit changes in behavior (irritability, depression, aberrant demeanor) after receiving diazepam. There have been reports of cats developing hepatic failure after receiving oral diazepam for several days. Clinical signs have been reported to occur 5-11 days after beginning oral therapy. Cats to receive diazepam should have baseline liver function tests. These should be repeated and the drug discontinued if emesis, lethargy, inappetence or ataxia develop.

Dogs may exhibit a contradictory response (CNS excitement) following administration of diazepam. The effects with regard to sedation and tranquilization are extremely variable with each dog. Because of this individual variation, diazepam is not an ideal sedating agent for this species.

**OVERDOSAGE**

When administered alone, diazepam overdoses are generally limited to significant CNS depression (confusion, coma, decreased reflexes, etc). Hypotension, respiratory depression, and cardiac arrest have been reported in human patients, but apparently are quite rare.

Treatment of acute toxicity consists of standard protocols for removing and/or binding the drug in the gut if taken orally, and supportive systemic measures. The use of analeptic agents (CNS stimulants such as caffeine) are generally not recommended. Flumazenil may be considered for adjunctive treatment of overdoses of benzodiazepines.

**DRUG INTERACTIONS**

Metabolism of diazepam may be decreased and excessive sedation may occur if given with the following drugs: **cimetidine, fluoxetine, erythromycin, isoniazid, ketoconazole, propranolol, metoprolol & valproic acid.**

If administered with other **CNS depressant agents (barbiturates, narcotics, anesthetics, etc.)** additive effects may occur.

**Antacids** may slow the rate, but not the extent of oral absorption; administer 2 hours apart to avoid this potential interaction.

The pharmacologic effects of **digoxin** may be increased; monitor serum digoxin levels or symptoms of toxicity.

**Rifampin** may induce hepatic microsomal enzymes and decrease the pharmacologic effects of benzodiazepines.

**Probenecid** may interfere with benzodiazepine metabolism in the liver, causing increased or prolonged effects.

Additionally, when the combination product with clidinium is used: Clidinium would be expected to have a similar drug interaction profile as atropine. The following drugs may enhance the activity of glycopyrrolate and its derivatives: **antihistamines, procainamide, quinidine, meperidine, benzodiazepines, phenothiazines.**
The following drugs may potentiate the adverse effects of clidinium and its derivatives: **primidone, disopyramide, and nitrates.**

Clidinium and its derivatives may enhance the actions of **nitrofurantoin, thiazide diuretics, or sympathomimetics.**

Clidinium may antagonize the actions of **metoclopramide.**

**Laboratory Interactions:** Patients receiving diazepam, may show false negative **urine glucose** results if using Diastix® or Clinistix® tests.

**DOSES**

**Dogs**

For treatment of seizures:

a) For cluster seizures or status epilepticus (for client treatment at home): If on phenobarbital, use diazepam at 2 mg/kg (using diazepam parenteral solution) per rectum. Administer at the onset of seizure and up to 3 times in a 24 hour period. Owners should stay with dog for one hour after administration. (Podell 2000)

b) For refractory status epilepticus using constant rate IV infusion: 0.1 - 0.5 mg/kg diluted in D5W. Rate administered per hour should be equal to the maintenance fluid requirement for the patient. Use with caution as diazepam can crystallize in solution and adsorb to PVC tubing.

For status or cluster seizure treatment at home: 0.5 - 2 mg/kg per rectum (Platt and McDonnell 2000)

c) For metaldehyde, strychnine or brucine induced seizures/tremors: 2 - 5 mg/kg IV (Bailey 1986a)

d) For methylxanthine (e.g., theophylline) induced seizures: 0.5 - 2.0 mg/kg IV (if unsuccessful use phenobarbital at 6 mg/kg IV q6-12h) (Hooser and Beasley 1986)

e) For salicylate toxicity induced seizures: 2.5 - 20 mg IV or PO (Handagama 1986)

f) Seizures secondary to CNS trauma: 0.25 - 0.5 mg/kg IV (Fenner 1986)

For white shaker dog syndrome:

a) 0.25 mg/kg PO tid-qid (Morgan 1988)

For Scotty cramp:

a) 0.5 - 2.0 mg/kg IV to effect or PO tid (Morgan 1988)

As a preanesthetic:

a) 0.1 mg/kg IV slowly (Morgan 1988)

For irritable colon syndrome:

a) 0.15 mg/kg PO tid (Morgan 1988)

For functional urethral obstruction/urethral sphincter hypertonus:

a) 2 - 10 mg q8h (Polzin and Osborne 1985); (Lane 2000)

b) 2 - 10 mg PO tid; 0.5 mg/kg IV (Chew, DiBartola, and Fenner 1986)

As a restraining agent/sedative:

a) 0.2 - 0.6 mg/kg IV (Morgan 1988)

b) 0.25 mg/kg PO q8h (Davis 1985a)

For separation anxiety:

a) 0.5 - 2.2 mg/kg PO prn (Morgan 1988)
Cats

As an appetite stimulant:

a) 0.05 - 0.15 mg/kg IV once daily to every other day or 1 mg PO once daily (Morgan 1988)
b) 0.05 - 0.4 mg/kg IV, IM or PO. After IV administration eating may begin a few seconds; have food readily available. (Booth 1988a)

Urine marking and anxiety:

a) 0.2 - 0.4 mg/kg PO q12-24h (start at 0.2 mg/kg PO q12h) (Overall 2000)
b) For spraying: 1 - 2.5 mg per cat PO q8-12h; sedation and ataxia should abate within several days. (Reisner and Houpt 2000)

For salicylate toxicity induced seizures:

a) 2.5 - 5 mg IV or PO (Handagama 1986)

For adjunctive treatment of feline psychogenic alopecia and dermatitis:

a) 1 - 2 mg PO bid (Walton 1986)

For treatment of seizure disorders:

a) 0.25 - 0.5 mg/kg PO q8-12h. To halt an ongoing seizure diazepam may be administered at 0.5 - 1 mg/kg IV. If cat has a history of receiving insulin glucose may be more beneficial. Do not use if cat has been exposed to chlorpyrifos as organophosphate toxicity may be potentiated (Shel 2000)
b) For oral maintenance therapy of seizures: As a second choice drug (after phenobarb): 0.5 - 1 mg/kg PO q12h (Quesnel 2000)

Functional urethral obstruction/urethral sphincter hypertonus:

a) 1 - 2.5 mg (total dose) PO q8h (Osborne, Kruger et al. 2000)
b) 1 - 2.5 mg (total dose) PO q8h OR 0.5 mg/kg IV (Lane 2000)

Rabbits/Rodents/Pocket Pets

a) Rabbits: Pre-anesthetic: 2 - 10 mg/kg IM; 1 - 5 mg/kg IM or IV. Give IV to effect for seizures. (Ivey and Morrissey 2000)
b) Rabbits: As a tranquilizer (to increase relaxation of lightly anesthetized animals and permit ET intubation): 1 mg/kg IV prn (Huerkamp 1995)
c) Hamsters, Gerbils, Mice, Rats: 3 - 5 mg/kg IM. Guinea pigs: 0.5 - 3 mg/kg IM (Adamcak and Otten 2000)

Cattle

Sedative in calves:

a) 0.4 mg/kg IV (Booth 1988a)

As a tranquilizer:

a) 0.55 - 1.1 mg/kg IM (Lumb and Jones 1984)

Treatment of CNS hyperactivity and seizures:

a) 0.5 - 1.5 mg/kg IM or IV (Bailey 1986b)

Horses

Note: ARCI UCGFS Class 2 Drug

For field anesthesia:

a) For field anesthesia: Sedate with xylazine (1.0 mg/kg IV; 2.0 mg/kg IM) given 5-10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either 1). Redose xylazine: up to half the original dose, 2) Add butorphanol (0.02 - 0.04 mg/kg IV).
b) Butorphanol can be given with the original xylazine if you suspect that the horse will be difficult to tranquilize (e.g., high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5-10 minutes. 3) **Diazepam** (0.03 mg/kg IV). Mix the diazepam with the ketamine. This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5-10 minutes. 4) Guaifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)

For seizures:
- a) Foals: 0.05 - 0.4 mg/kg IV; repeat in 30 minutes if necessary;
- Adults: 25 - 50 mg IV; repeat in 30 minutes if necessary. (Sweeney and Hansen 1987)

Treatment of seizures secondary to intra-arterial injection of xylazine or other similar agents:
- a) 0.10 - 0.15 mg/kg IV (Thurmon and Benson 1987)

As an appetite stimulant:
- a) 0.02 mg/kg IV; immediately after dosing offer animal food. Keep loud noises and distractions to a minimum. If effective, usually only 2-3 treatments in a 24-48 hour period is required. (Ralston 1987)

**Swine**

For tranquilization:
- a) 5.5 mg/kg IM (will develop posterior ataxia in 5 minutes and then recumbency within 10 minutes) (Booth 1988a)
- b) 0.55 - 1.1 mg/kg IM (Lumb and Jones 1984)

For sedation prior to pentobarbital anesthesia:
- a) 8.5 mg/kg IM (maximized at 30 minutes; reduces pentobarbital dose by 50%) (Booth 1988a)

For treatment of CNS hyperactivity and seizures:
- a) 0.5 - 1.5 mg/kg IM or IV (Howard 1986)

**Sheep**

As a tranquilizer:
- a) 0.55 - 1.1 mg/kg IM (Lumb and Jones 1984)

**Goats**

For Bermuda grass induced toxicosis and tremors:
- a) 0.8 mg/kg IV (Booth 1988a)

To stimulate appetite:
- a) 0.04 mg/kg IV; offer food immediately, duration of effect may last up to 45 minutes. (Booth 1988a)

**Birds**

For adjunctive therapy of pain control (w/analgesics):
- a) 0.5 - 2 mg/kg IV or IM (Clyde and Paul-Murphy 2000)

**MONITORING PARAMETERS**

Horses should be observed carefully after receiving this drug. Cats receiving diazepam should have baseline liver function tests. Repeat and d/c drug if emesis, lethargy, inappetence or ataxia develop. When used for seizure control in cats, one author (Quesnel 2000) recommends obtaining serum level 5 days after beginning therapy. Goal is to achieve levels in the therapeutic range of 500 - 700 nmol/L (500 - 700 ng/ml).
CLIENT INFORMATION
Keep out of reach of children and in tightly closed containers.

DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES
Veterinary-Approved Products

Human-Approved Products
Diazepam oral tablets 2 mg, 5 mg, 10 mg; Valium® (Roche); Generic; (Rx)
Diazepam oral solution 1 mg/ml in 500 ml, & UD 5 & 10 ml, 1 mg/ml in 500 ml containers, UD 5 & 10 ml and 5 & 10 mg patient cups, 5 mg/ml in 30 ml dropper bottle; i. Diazepam® & Diazepam Intensol®; (Roxane); Generic (Rx)
Diazepam Injection 5 mg/ml in 1 & 2 ml cartridges, 2 ml amps & syringes & 1, 2, &10 ml vials, 2 ml disposable syringes & Tel-E-Jects; Valium® (Roche); Generic; (Rx)
Diazepam Rectal Gel 2.5 mg, 5 mg & 10 mg (all pediatric) & 15 mg & 20 mg (both adult); in twin packs with molded tips in 2 lengths; Diastat® (Elan) (Rx)
Diazepam is a Class-IV controlled substance.

DORAMECTIN

PRESCRIBER HIGHLIGHTS
- Injectable avermectin antiparasiticide labeled for use in cattle
- Manufacturer warns about using in other species
- IM injections may cause muscle blemishes
- Not labeled for female dairy cattle (20 mos or older)
- At labeled dosage, slaughter withdrawal = 35 days

CHEMISTRY/STORAGE/StABILITY/COMPATIBILITY
An avermectin antiparasitic compound, doramectin is isolated from fermentations from the soil organism Streptomyces avermitilis. The commercially available injectable solution is a colorless to pale yellow, sterile solution. The injectable solution should be stored below 86°F (30°C).

PHARMACOLOGY
The primary mode of action of avermectins like doramectin is to affect chloride ion channel activity in the nervous system of nematodes and arthropods. Doramectin binds to receptors that increase membrane permeability to chloride ions. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods and causes paralysis and death of the parasites. Avermectins also enhance the release of gamma amino butyric acid (GABA) at presynaptic neurons. GABA acts as an inhibitory neurotransmitter and blocks the post-synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber in arthropods. Avermectins are generally not toxic to mammals as they do not have glutamate-gated chloride channels and these compounds do not readily cross the blood-brain barrier where mammalian GABA receptors occur.

USES/INDICATIONS
Doramectin injection is indicated for the treatment and control of the following endo- and ectoparasites in cattle: roundworms (adults and some fourth stage larvae)-Ostertagia ostertagi (including inhibited larvae), O. lyrata, Haemonchus placei, Trichostrongylus axei, T. colubriformis, T. longispicularis, Cooperia oncophora, C. pectinata, C. punctata, C. sumabada (syn. mcmasteri), Bunostomum phlebotomum, Strongyloides papillosus, Oesophagostomum radiatum, Trichuris spp.; lungworms (adults and fourth stage larvae)-Dictyocaulus viviparus; eyeworms (adults)-Thelazia spp.; grubs (parasitic stages)-Hypoderma bovis, H. lineatum; lice-Haematopinus eurysternus, Linognathus vituli, Solenopotes capillatus; and mange mites-Psoroptes bovis, Sarcoptes scabiei.
The manufacturer states the doramectin protects cattle against infection or reinfection with *Ostertagia ostertagi* for up to 21 days.

**PHARMACOKINETICS**

After subcutaneous injection, the time to peak plasma concentration in cattle is about 5 days. Bioavailability is for practical purposes, equal with SC and IM injections.

**CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY**

The manufacturer warns to not use in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Studies performed in breeding animals (bulls, and cows in early and late pregnancy), at a dose of 3X recommended had no effect on breeding performance.

**ADVERSE EFFECTS/WARNINGS**

No listed adverse effects. Intramuscular injections may have a higher incidence of injection site blemishes at slaughter than do subcutaneous injections.

**OVERDOSAGE**

In field trials, no toxic signs were seen in cattle given up to 25X the recommended dose. In breeding animals (bulls, and cows in early and late pregnancy), a dose 3 times the recommended dose had no effect on breeding performance.

**DRUG INTERACTIONS**

None noted.

**DOSES**

**Cattle**

For labeled indications: 200 mcg/kg (1 ml per 110 lb. body weight) SC or IM. Injections should be made using 16 to 18 gauge needles. Subcutaneous injections should be administered under the loose skin in front of or behind the shoulder. Intramuscular injections should be administered into the muscular region of the neck. Beef Quality Assurance guidelines recommend subcutaneous administration as the preferred route. (Label Directions; Dectomax®-Pfizer)

**MONITORING PARAMETERS**

Efficacy

**CLIENT INFORMATION/WITHDRAWAL TIMES**

Cattle must not be slaughtered for human consumption within 35 days of treatment. Not for use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in preruminating calves. Should not be used in calves to be processed for veal.

**Veterinary Approved Products**

Doramectin 10 mg/ml Injectable Solution in 100 ml, 250 ml, and 500 ml multi-dose vials; Dectomax® (Pfizer); (OTC). Approved for use in cattle & swine At labeled doses: Slaughter Withdrawal: cattle = 45 days, swine = 24 days. Do not use in female dairy cattle 20 months of age or older or in calves to be used for veal. A withdrawal period has not been established in preruminating calves.

Doramectin 5 mg/ml Injectable Solution in 250 ml, 1 L, 2.5 L & 5 L multi-dose containers. Dectomax® Pour-On (Pfizer) (OTC). Approved for use in cattle. Slaughter withdrawal =45 days. Not for use in female dairy cattle 20 months of age or older. A withdrawal period has not been established in preruminating calves. Do Not use in calves to be used for veal.
**DOXAPRAM HCl**

**Prescriber Highlights**
- CNS stimulant usually used to stimulate respirations in newborns or after anesthesia
- Not a substitute for aggressive artificial (mechanical) respiratory support when required
- Possible contraindications: receiving mechanical ventilation, hypersensitivity, seizure disorders, head trauma/CVA, uncompensated heart failure, severe hypertension, respiratory failure secondary to neuromuscular disorders, airway obstruction, pulmonary embolism, pneumothorax, acute asthma, dyspnea, or whenever hypoxia is not associated with hypercapnia.
- Caution: History of asthma, arrhythmias, or tachycardias. Extreme caution pts. w/ cerebral edema or increased CSF pressure, pheochromocytoma or hyperthyroidism.
- Avoid using a single injection site for a prolonged period of time or extravasation when administering intravenously.
- Adverse effects: hypertension, arrhythmias, seizures, and hyperventilation leading to respiratory alkalosis

**Chemistry**
Doxapram HCl is a white to off-white, odorless, crystalline powder that is stable in light and air. It is soluble in water, sparingly soluble in alcohol and practically insoluble in ether. Injectable products have a pH from 3.5-5. Benzyl alcohol or chlorobutanol is added as a preservative agent in the commercially available injections.

**Storage/Stability/Compatibility**
Store at room temperature and avoid freezing solution. Do not mix with alkaline solutions (e.g., thiopental, aminophylline, sodium bicarbonate). Doxapram is physically compatible with D$_5$W or normal saline.

**Pharmacology**
Doxapram is a general CNS stimulant, with all levels of the CNS affected. The effects of respiratory stimulation are a result of direct stimulation of the medullary respiratory centers and possibly through the reflex activation of carotid and aortic chemoreceptors. Transient increases in respiratory rate and volume occur, but increases in arterial oxygenation usually do not ensue. This is because doxapram usually increases the work associated with respirations with resultant increased oxygen consumption and carbon dioxide production.

**Pharmacokinetics**
Little pharmacokinetic data appears to be published for domestic animals. Onset of effect in humans and animals after IV injection usually occurs within 2 minutes. The drug is well distributed into tissues. In dogs, doxapram is rapidly metabolized and most is excreted as metabolites in the urine within 24-48 hours after administration. Small quantities of metabolites may be excreted up to 120 hours after dosing.

**Uses/Indications**
The manufacturer of Dopramp®-V lists the following indications:

For Dogs, Cats, and Horses: To stimulate respiration during and after general anesthesia and/or to speed awakening and reflexes after anesthesia.

For Neonatal Dogs and Cats: Initiate or stimulate respirations following dystocia or cesarean section.

Doxapram also has been used for treatment of CNS depression in food animals (not approved) and has been suggested as a treatment of respiratory depression in small animals caused by reactions to radiopaque contrast media or for barbiturate overdose (see precautions below).

**Contraindications/Precautions**
Doxapram should not be used as a substitute for aggressive artificial (mechanical) respiratory support in instances of severe respiratory depression.

Contraindications from the human literature include: seizure disorders, head trauma, uncompensated heart failure, severe hypertension, cardiovascular accidents, respiratory failure secondary to neuromuscular disorders, airway obstruction, pulmonary embolism, pneumothorax, acute asthma, dyspnea, or whenever hypoxia is not associated with hypercapnia.
Doxapram should be used with caution in patients with history of asthma, arrhythmias, or tachycardias. It should be used with extreme caution in patients with cerebral edema or increased CSF pressure, pheochromocytoma or hyperthyroidism. Patients who have a history of hypersensitivity to the drug or are receiving mechanical ventilation should not receive doxapram. The above contraindications/precautions are not listed in the veterinary product literature provided by the manufacturer.

Avoid the use of a single injection site for a prolonged period of time or extravasation when administering intravenously. However, subcutaneous injection has been recommended for use in neonatal feline and canine patients.

**ADVERSE EFFECTS/Warnings**

Hypertension, arrhythmias, seizures, and hyperventilation leading to respiratory alkalosis has been reported. These effects are most probable with repeated or high doses. The drug reportedly has a narrow margin of safety when used in humans.

Safety of doxapram has not been established in pregnant animals. The potential risks versus benefits should be weighed before using.

**OVERDOSAGE**

Symptoms of overdosage include: hypertension, skeletal muscle hyperactivity, tachycardia, and generalized CNS excitation including seizures. Treatment is supportive. Drugs such as short acting IV barbiturates may be used to help decrease CNS hyperactivity. Oxygen therapy may be necessary.

**DRUG INTERACTIONS**

Additive pressor effects may occur with **sympathomimetic** agents.

Doxapram may mask the effects of **muscle relaxant** drugs.

Doxapram may increase epinephrine release; therefore use should be delayed for approximately 10 minutes after discontinuation of anesthetic agents (*e.g.*, **halothane, enflurane**) that have been demonstrated to sensitize the myocardium to catecholamines.

**Doses**

**Dogs, Cats**

a) 1 - 5 mg/kg IV; may repeat prn. To stimulate respirations in newborns: 1- 2 drops under tongue or 0.1 ml IV in umbilical vein (should be used with caution if product contains benzyl alcohol as a preservative). (Package Insert; Dopram®-V - Robins)

b) Cats: 5 - 10 mg/kg IV (Boothe 1990)

**Rabbits/Rodents/Pocket Pets**

For respiratory depression:

a) **Rabbits**: 2 - 5 mg/kg SC or IV q15 minutes

b) **Mice, Rats, Gerbils, Hamsters**: 5 - 10 mg/kg IV. **Guinea pigs**: 5 mg/kg IV. **Chinchillas**: 2 - 5 mg/kg IV (Adamcak and Otten 2000)

**Cattle, Swine**

a) 5 - 10 mg/kg IV (Howard 1986)

**Horses**

Note: ARCI UCGFS Class 2 Drug

a) 0.5 - 1 mg/kg IV at 5 minute intervals (do not exceed 2 mg/kg in foals); For foal resuscitation: 0.02 - 0.05 mg/kg/min IV (Robinson 1987)
**MONITORING PARAMETERS**

1) Respiratory rate  
2) Cardiac rate and rhythm  
3) Blood gases if available and indicated  
4) CNS level of excitation  
5) Blood pressure if possible and indicated

**CLIENT INFORMATION**

This agent should be used in an inpatient setting or with direct professional supervision.

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**

Doxapram HCl for Injection: 20 mg/ml; 20 ml multi-dose vial; Dopram-V® (Fort Dodge); (Rx) Approved for use in dogs, cats & horses

**Human-Approved Products**

Doxapram HCl for Injection: 20 mg/ml in 20 ml vial; Dopram® (Robins); generic, (Rx)

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**ETODOLAC**

**PRESCRIBER HIGHLIGHTS**

- NSAID (oral) used in dogs, relatively few adverse effects and labeled for once daily
- Contraindications: Hypersensitive. Caution: pts w/ preexisting or occult GI, hepatic, renal, cardiovascular or hematologic abnormalities.
- Safe use not established for dogs less than 12 months of age or in breeding, pregnant, or lactating dogs
- Adverse Effects: vomiting, diarrhea, lethargy, and hypoproteinemia.
- Drug interactions

**CHEMISTRY/STORAGE/StABILITY/COMPATIBILITY**

An indole acetic acid derivative non-steroidal antiinflammatory agent (NSAID), etodolac occurs as a white, crystalline compound that is insoluble in water, but soluble in alcohol or DMSO. Etodolac has a chirally active center with a corresponding S (+) enantiomer and an R (-) enantiomer. The commercially available product is supplied as a racemic mixture of the forms.

The commercially available veterinary tablets should be stored at controlled room temperature (15-30°C).

**PHARMACOLOGY**

Like other NSAIDs, etodolac has analgesic, antiinflammatory and antipyretic activity. Etodolac appears to be more selective for inhibition of cyclooxygenase-2 than cyclooxygenase-1. This means that the drug should possess greater inhibition of the prostaglandins involved with pain and inflammation than those involved with cytoprotection of the GI tract and renal tissue. Etodolac is also thought to inhibit macrophage chemotaxis, which may explain some of its antiinflammatory activity.

**USES/INDICATIONS**

Etodolac is labeled for the management of pain and inflammation associated with osteoarthritis in dogs. It may find uses however for a variety of conditions where pain and/or inflammation should be treated.
PHARMACOKINETICS
The S (+) enantiomer is thought to provide the bulk of the pharmacologic activity, but the drug is supplied as a racemic mixture. Pharmacokinetic studies that measure both forms as one are not very relevant clinically. After oral administration to healthy dogs, etodolac is rapidly and nearly completely absorbed. The presence of food may alter the rate, but not the extent of absorption. Peak serum levels occur about 2 hours post dosing. Etodolac is highly bound to serum proteins. The drug is primarily excreted via the bile into the feces. Glucuronide conjugates have been detected in the bile but not the urine. Elimination half life in dogs varies depending whether food is present in the gut, which may affect the rate of enterohepatic circulation of the drug. These values range from about 8 hours (fasted) to 12 hours (non-fasted).

CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY
Etodolac is contraindicated in dogs previously found to be hypersensitive to it. It should be used with caution in dogs with preexisting or occult GI, hepatic, cardiovascular or hematologic abnormalities as NSAIDs may exacerbate these conditions. Patients may be more susceptible to renal injury from etodolac if they are dehydrated, on diuretics, or have preexisting renal, hepatic or cardiovascular dysfunction.

Safety of etodolac has not been established in dogs less than 12 months of age. Safe use has also not been established in breeding, pregnant, or lactating dogs. Use only when the benefits clearly outweigh the potential risks of use in these animals.

ADVERSE EFFECTS/WARNINGS
In clinical field studies, etodolac's primary adverse effect was vomiting/regurgitation, reported in about 5% of dogs tested. Diarrhea, lethargy, and hypoproteinemia were also reported in a small number of dogs. Urticaria, behavioral changes and inappetence were reported in less than 1% of dogs treated. It must be remembered however, that as the drug is used in many more dogs for significant periods of time, additional adverse effects may surface.

The manufacturer warns to terminate therapy if inappetence, vomiting, fecal abnormalities or anemia are observed.

OVERDOSEAGE
Limited information is available, but in a safety study where dogs were given 40 mg/kg/day (2.7X) GI ulcers, weight loss, emesis and local occult blood were noted. Doses of 80 mg/kg/day (5.3X), caused 6 of 8 dogs to either die or become moribund secondary to GI ulceration. It should be noted that these were not single dose overdoses. However, they do demonstrate that there is relatively narrow therapeutic window for the drug in dogs and that doses should be carefully determined (i.e., do not confuse mg/kg dosages with mg/lb).

DRUG INTERACTIONS
Note: Although the manufacturer does not list any specific drug interactions in the package insert, it does caution to avoid or closely monitor etodolac's use with other drugs, especially those that are also highly protein bound. It also recommends closely monitoring, or avoiding using etodolac with any other ulcerogenic drugs (e.g., corticosteroids, other NSAIDs).

In humans, there are many interactions possible with NSAIDs. Because clinical experience is limited in dogs, the following may or may not be clinically significant. Because etodolac is highly bound to plasma proteins, it may displace other highly bound drugs. Increased serum levels and duration of actions of phenytoin, valproic acid, oral anticoagulants, other anti-inflammatory agents, salicylates, sulfonamides, and the sulfonylurea antidiabetic agents may occur.

When aspirin is used concurrently with etodolac, plasma levels of etodolac could decrease and an increased likelihood of GI adverse effects (blood loss) could occur. Concomitant administration of aspirin with etodolac cannot be recommended.

Probenecid may cause a significant increase in serum levels and half-life of etodolac.

Serious toxicity has occurred when NSAIDs have been used concomitantly with methotrexate; use together with extreme caution.

Etodolac may reduce the saluretic and diuretic effects of furosemide and increase serum levels of digoxin. Use with caution in patients with severe cardiac failure.
DOSES

Dogs

a) For treatment of pain and inflammation associated with osteoarthritis: 10 - 15 mg/kg PO once daily. Dogs less than 5 kg cannot be accurately dosed with EtoGesic®. Adjust dose to obtain satisfactory response, but do not exceed 15 mg/kg. For long term therapy, reduce dose level to minimum effective dosage. (Package Insert; EtoGesic®-Fort Dodge)

b) 5 - 15 mg/kg PO once daily (Hardie 2000)

MONITORING PARAMETERS

Efficacy and adverse effects

CLIENT INFORMATION

Because etodolac is a relatively new drug for use in dogs, clients should be cautioned to monitor and report any significant change in the animal's health to the veterinarian. This author recommends monitoring etodolac similarly to carprofen, namely: 1) Baseline (especially in geriatric dogs or dogs with chronic diseases or those where prolonged treatment is likely): physical exam, CBC, Serum chemistry panel (including liver and renal function tests), UA. It is recommended to reassess liver enzymes at one week of therapy. Should elevation occur, recommend discontinuing the drug. 2) Clinical efficacy 3) Signs of potential adverse reactions: inappetence, diarrhea, mucoid feces, vomiting, melena, polyuria/polydipsia, anemia, jaundice, lethargy, behavior changes, ataxia or seizures 4) Chronic therapy: Consider repeating CBC, UA and serum chemistries on an ongoing basis.

DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS

Veterinary-Approved Products

Etodolac 150 mg and 300 mg scored tablets in bottles of 30 & 90; EtoGesic® (Fort Dodge); (Rx) Approved for use in dogs. Do not use in cats.

Human-Approved Products

Etodolac 200 mg, 300 mg oral capsules, 400 mg, 500 mg tablets & 400 mg, 500 mg & 600 mg extended release tablets; Lodine® & Lodine XL® (Wyeth-Ayerst); (Rx)

FENTANYL CITRATE/DROPERIDOL

PRESCRIBER HIGHLIGHTS

- Class-II opiate analgesic/neuroleptic combination used parenterally primarily in small animals
- Contraindications: Use extreme caution when additional respiratory, circulatory or CNS depression would be deleterious. Use caution in geriatric, very ill or debilitated patients and those with a preexisting respiratory problem.
- Adverse Effects: Dose related respiratory, CNS and circulatory depression (bradycardia). Also urine retention, salivation, panting, constipation, dysphoria or agitation.
- Do not give IV too rapidly. Do not confuse veterinary and human products (different concentrations).
- Lab values (amylase, lipase) may be altered

CHEMISTRY

Fentanyl citrate, a very potent opiate agonist, occurs as a white, crystalline powder. It is sparingly soluble in water and soluble in alcohol. It is odorless and tasteless (not recommended for taste test because of extreme potency) with a $pK_a$ of 8.3 and a melting point between 147°-152°C.

Droperidol, a butyrophenone neuroleptic agent, occurs as a white to light tan, amorphous or macrocrystalline powder. One gram is soluble in 10 L of water and 600 ml of alcohol.
It is odorless and tasteless (not recommended for taste test because of extreme potency) with a pKₐ of 7.6 and a melting point between 144°-148°C.

The combination commercially available products (Innovar® and Innovar®-Vet) have pH's of approximately 3-3.5.

**Storage/Stability/Compatibility**

Intact ampules and vials should be stored at room temperature and out of light. Innovar® has been reported to be physically compatible when mixed with the following agents: D5W, lactated Ringer’s, D5 in lactated Ringer’s, normal saline, benzquinamide, glycopyrrolate, heparin sodium, hydrocortisone sodium succinate, potassium chloride, and sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used, and it is suggested to consult specialized references (e.g., Handbook on Injectable Drugs by Trissel; see bibliography) for more specific information.

**Pharmacology**

The butyrophenones (e.g., droperidol) as a class cause tranquillization and sedation (sedation may be less so than with the phenothiazines), anti-emetic activity, reduced motor activity, and inhibition of CNS catecholamines (dopamine, norepinephrine). The pharmacology of the opiate agonists are discussed in more detail in the monograph, Narcotic (opiate) Agonist Analgesics. When used together droperidol/fentanyl will induce considerable neuroleptanalgesia. The actions of droperidol are said to potentiate the analgesic effects of fentanyl.

In dogs, Innovar® can cause decreased heart rates secondary to increased vagal tone and a decrease in arterial blood pressures. In cats, increased heart rates can be noted as well as a decrease in blood pressure.

**Uses/Indications**

Droperidol/fentanyl is approved in veterinary medicine only for use in the dog. It is indicated alone as a combination analgesic/tranquilizer for minor surgical, dental and orthopedic procedures and manipulations of short duration or (in combination with other general anesthetics) for major surgical procedures. It is considered by some clinicians to be the drug of choice as a chemical restraining agent in aggressive dogs. Fentanyl/droperidol has also been used as a tranquilizer/analgesic in cats.

**Pharmacokinetics**

No veterinary references regarding the pharmacokinetics of these agents were located. The onset of action after IV administration in dogs occurs within minutes and slightly longer after IM administration. In cats, after SC injection, the onset of effect occurs within 20-30 minutes. Both drugs are metabolized in the liver and are eliminated in the urine (both as metabolites and unchanged drug). Duration of effect (at usual doses) after IM administration in dogs is generally 30-40 minutes, most animals will be sedated for several hours after anesthetic actions have ceased. Approximately 1.5 hours are necessary for dogs to recover after IV administration.

**Contraindications/Precautions**

This combination is not approved for use in food producing animals. Use cautiously with other CNS depressants, dosages of other anesthetics may need to be reduced when given after Innovar®. Pentobarbital dosages (for anesthesia) must be reduced for 4 hours after Innovar®. Perivascular injections may be irritating to surrounding tissue; avoid extravasation. Australian terriers may be resistant to the neuroleptanalgesic effects of Innovar® at usual doses, but exhibit side effects of tremors, excessive salivation, bradycardia, and diarrhea.

**Adverse Effects/Warnings**

In dogs, adverse effects with Innovar® are usually dose related and most commonly observed at the higher end of the dosing range. They include defecation, flatulence, respiratory depression, panting, nystagmus, head tremors, pain after IM injection, and personality changes (rare). Bradycardia and salivation can be seen if the animal is not pretreated with atropine or other anticholinergic agents. Animals may show a startle reaction following stimuli (e.g., loud noises) and rarely seizures may develop.

A syndrome described as "woody chest" can occur after rapid IV administration. The thoracic musculature becomes very rigid and interferes with normal breathing, but can be treated with naloxone, or mechanical ventilation and muscle relaxant agents.
CNS stimulation, ataxia, and abnormal behavior (squealing, "goose-stepping", stumbling into objects) can be seen in pigs following IM administration.

**IM or SC injection may cause irritation and pain at the injection site.**

### OVERDOSAGE

Overdosage may produce profound respiratory and/or CNS depression in most species. Newborns may be more susceptible to these effects than adult animals. Other toxic effects may include cardiovascular collapse, tremors, neck rigidity, and seizures. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of fentanyl are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression. 4-aminopyridine has been demonstrated to act as an antagonist to droperidol in the dog at a dose 0.5 mg/kg IV, but it is not available in an approved commercially available dosage form.

Pentobarbital (6.6 mg/kg) has been suggested as a treatment for CNS effects (seizures) and extension and rigidity of the neck. Extreme caution must be used as barbiturates and narcotics can have additive respiratory depression effects.

### DRUG INTERACTIONS

For opiates (fentanyl): Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with opiates. Opiate analgesics are contraindicated in patients receiving monamine oxidase (MAO) inhibitors (rarely used in veterinary medicine) for at least 14 days after receiving MAO inhibitors (in humans).

For butyrophenones (droperidol): CNS depressant agents (barbiturates, narcotics, anesthetics, etc.) may cause additive CNS depression if used with butyrophenones.

### LABORATORY INTERACTIONS

Plasma amylase and lipase values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

### DOSES

**Caution:** Doses are for the veterinary product (*Innovar-Vet®*) which is 8X more concentrated than the human labeled product (*Innovar®*).

#### Dogs

To prevent bradycardia and excessive salivation, atropine (0.045 mg/kg SC) or glycopyrrolate should generally be given 15 minutes prior to IV administration or concurrently with IM dose.

- a) For analgesia and tranquillization: 1 ml per 6.8 - 9.1 kg (0.11 - 0.15 ml/kg) IM or 1 ml per 11.35 - 27 kg (0.037 - 0.088 ml/kg) IV (Package Insert: *Innovar® Vet-P/M*; Mallinckrodt)
- b) For general anesthesia: 1 ml per 18.2 kg (40 lbs.) IM; or 1 ml per 11.35 - 27.3 kg (25 - 60 lbs) IV. Followed by a general anesthetic (barbiturate, halothene, etc.) in 10 minutes after IM injection and 1 minute after IV injection. (Package Insert; *Innovar® Vet-P/M*; Mallinckrodt)
- c) For tranquillization: 0.3 - 0.5 ml per 55 kg IV

As a preanesthetic: 1 ml per 20 kg IM

As an anesthetic for gastric dilatation: 1 ml per 10 - 30 kg.; dilute in 20 ml of saline, give IV slowly (Morgan 1988)

#### Cats

- a) 1 ml/9 kg body weight (*Innovar®-Vet*) SC; maximal effects occur between 30-60 minutes (Grandy and Heath 1987)
MONITORING PARAMETERS
1) Level of neuroleptanalgesia
2) Respiratory/cardiovascular status

CLIENT INFORMATION
This drug should only be used by professionals familiar with its effects in a setting where adequate respiratory support can be performed.

DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES
Note: The veterinary approved product that was formerly available (Innovar®-Vet) was 8 times more concentrated than the human approved product. Do not confuse the two.

Veterinary-Approved Products: None.

Human-Approved Products
0.05 mg fentanyl (as citrate) and 2.5 mg droperidol per ml in 2 & 5 ml amps & vials
Fentanyl Citrate and Droperidol® (Astra) (Rx) (CII)

FENTANYL, TRANSDERMAL
FENTANYL CITRATE, INJECTABLE

Note: A separate monograph for fentanyl/droperidol (Innovar®) follows this one.

PRESCRIBER HIGHLIGHTS
- Class-II opiate analgesic used parenterally and transdermally in small animals
- Contraindications: Use extreme caution when additional respiratory, circulatory or CNS depression would be deleterious. Use caution in geriatric, very ill or debilitated patients and those with a preexisting respiratory problem.
- Adverse Effects: Dose related respiratory, CNS and circulatory depression (bradycardia). Also, rashes at the patch site, urine retention, constipation, dysphoria or agitation.
- Do not cut patches. Dispose of properly.
- Lab values (amylase, lipase) may be altered

CHEMISTRY
Fentanyl citrate, a very potent opiate agonist, occurs as a white, crystalline powder. It is sparingly soluble in water and soluble in alcohol. It is odorless and tasteless (not recommended for taste test because of extreme potency) with a pKₐ of 8.3 and a melting point between 147°-152°C.

STORAGE/StABILITY/COMPATIBILITY
Fentanyl transdermal patches should be stored at temperatures less than 25°C and applied immediately after removing from the individually sealed package. Fentanyl injection should be stored protected from light.

PHARMACOLOGY
Fentanyl is a mu opiate agonist. The pharmacology of the opiate agonists are discussed in more detail in the monograph, Narcotic (opiate) Agonist Analgesics.

USES/INDICATIONS
In veterinary medicine, fentanyl injection and transdermal patches are used primarily in dogs and cats and have been shown to be useful for the adjunctive control of postoperative pain and in the control of severe pain associated with chronic pain, dull pain and non-specific, widespread pain (e.g., associated with cancer, pancreatitis, aortic thromboemboli, peritonitis, etc.). Although clinical use in dogs and cats has been limited, thus far transdermal fentanyl has overall been clinically effective and has not had substantial adverse effect problems.
In humans, significant respiratory depression with use of the patches after surgery has precluded from using them post-operatively, but this has not been a significant problem in veterinary medicine.

**PHARMACOKINETICS**

There have been limited pharmacokinetic studies performed with transdermal fentanyl patches in dogs and cats. While therapeutic levels of fentanyl are attained, there is a significant interpatient variability with both the time to achieve therapeutic levels and the levels themselves. Cats tend to achieve therapeutic levels faster than do dogs and in dogs, the patch should be applied 24 hours in advance of need if possible, minimum of 12 hours pre-need. Most cats attain therapeutic benefit in about 6 hours after application. While applied, duration of action persists for at least 72 hours (usually for at least 104 hours). Duration of action is generally longer in cats than in dogs.

**CONTRAINDICATIONS/PRECAUTIONS**

Use cautiously with other CNS depressants, dosages of other opiates may need to be reduced when given with fentanyl transdermal, particularly several hours after application of the patch. Transdermal fentanyl should be used cautiously in geriatric, very ill or debilitated patients and those with a preexisting respiratory problem. Febrile patients may have increased absorption of fentanyl and will require increased monitoring should application be made.

Safe use in pregnancy has not been established.

**ADVERSE EFFECTS/WARNINGS**

Respiratory depression and bradycardia associated with fentanyl patches are the most concerning adverse effects, but incidence of these effects have not been widespread thus far when used alone (without other opiates or other respiratory and cardiodepressant medications). Rashes at the patch site have been reported and should they occur, the patch should be removed. If an additional patch is warranted, a different site should be chosen. Urine retention and constipation may occur. Consider removing patch in patients developing a fever after application, as fentanyl absorption may increase. Some patients exhibit dysphoria or agitation after application; acepromazine or other mild tranquilizer may alleviate dysphoria.

**OVERDOSAGE**

Overdosage may produce profound respiratory and/or CNS depression in most species. Newborns may be more susceptible to these effects than adult animals. Other toxic effects may include cardiovascular collapse, tremors, neck rigidity, and seizures. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of fentanyl are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

**DRUG INTERACTIONS**

For opiates (fentanyl): Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with opiates. Opiate analgesics are contraindicated in patients receiving monamine oxidase (MAO) inhibitors (rarely used in veterinary medicine) for at least 14 days after receiving MAO inhibitors (in humans).

**LABORATORY INTERACTIONS**

Plasma amylase and lipase values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**DOSES**

**Dogs**

**Fentanyl Injectable:**

a) For perioperative pain: 5 mcg/kg IV plus 3 - 6 mcg/kg/hour IV infusion (Pascoe 2000)

b) For initial management of acute (moderate to severe) pain: 0.004 - 0.01+ mg/kg (4 - 10 mcg/kg) IV bolus and then 0.001 - 0.004 mg/kg/hour (4 - 10 mcg/kg/hour) constant rate IV infusion. (Mathews 2000)
Fentanyl Transdermal:

Note: There is significant interpatient variability on the response of the transdermal product.

a) The following dosage regimen is used at the University of Minnesota Veterinary Teaching Hospital and is adapted from a presentation by Dr. Lynelle Graham:

In acutely painful patients provide alternative analgesia (injectable opioids, epidural opioids or constant rate infusion of opioids) until "lag" phase is completed (usually 6 hours in cats and a minimum of 12 hours in dogs).

Patch Size:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Fentanyl Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Dogs ** (&lt;5kg) &amp; Cats</td>
<td>25 mcg/hr</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Dogs: 5-10 kg</td>
<td>25 mcg/hr</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Dogs: 10-20 kg</td>
<td>50 mcg/hr</td>
<td>5 mg</td>
</tr>
<tr>
<td>Dogs: 20-30 kg</td>
<td>75 mcg/hr</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Dogs: &gt;30 kg</td>
<td>100 mcg/hr</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

** Small dogs and cats may be dosed with 1/2 patch, but the patch should not be cut in half! Cover 1/2 the gel membrane with tape. "Half-patch dosing" is suggested for pediatric, geriatric and systemically ill cats and small dogs.

Patch may be placed either at dorsal or lateral cervical area, the lateral thorax or the inguinal area. If the neck is used, collars/leashes cannot be placed over the patch. Thorax is easily used and contact maximized (especially in cats), but can be difficult to bandage and the bald spot and change in hair growth/color may bother some clients. Inguinal area may be difficult to see and assess and some patients can lick/chew at the area. Regardless of site chosen, it must be clean and dry at the time of application and while the patch is attached. Do not place where a heating pad may come into contact. Site should be closely clipped with at least a 1 cm margin around the patch. Do not shave or surgically prepare the site. After clipping, wipe with damp cloth to remove small hairs and skin debris; do not scrub or surgically prepare the site. Allow to completely dry.

Remove occlusive membrane from patch by folding back the edge and gently tear away the membrane to expose the sticky surface. Be careful not to expose your skin to the gel surface. Place patch over clipped area and hold it in place for 2-3 minutes to maximize adherence. Use a slightly padded bandage or transparent dressing used with medical adhesive spray to assure adherence and to keep it dry. Check every few hours to ensure proper placement and adherence.

Dispose of used patches in a safe and effective manner.

Cats

Fentanyl Injectable:

a) For perioperative pain: 2 - 3 mcg/kg IV plus 2 - 3 mcg/kg/hour IV infusion (Pascoe 2000)

b) For initial management of acute (moderate to severe) pain: 0.004 - 0.01+ mg/kg (4 - 10 mcg/kg) IV bolus and then 0.001 - 0.004 mg/kg/hour (4 - 10 mcg/kg/hour) constant rate IV infusion. (Mathews 2000)

Fentanyl Transdermal: See above (dog dose)

Rabbits/Rodents/Pocket Pets

Fentanyl Injectable:

a) For perioperative pain: 5 - 20 mcg/kg IV bolus (30-60 minute duration; causes sedation and respiratory depression) (Ivey and Morrissey 2000)

Fentanyl Transdermal:

a) Rabbits for postoperative analgesia: 1/2 small patch (25 mcg/hr) per medium sized rabbit
(3 kg) every 3 days. Do not cut patch (Ivey and Morrisey 2000)

**MONITORING PARAMETERS**
1) Analgesic efficacy 2) Heart rate and respiratory rate

**CLIENT INFORMATION**
Explain carefully to clients how to apply (if applicable), remove and dispose of patches. Should accidental human skin contact occur, wash with water (only; no soap, etc.). Consider making application, removal and disposal an outpatient procedure, thereby bypassing concerns with clients.

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products:** None:

**Human-Approved Products**
- Injectable: 0.05 mg/ml (as the citrate salt) in 2, 5, 10, 20 ml ampules; 20, 30, 50 ml vials; 2 and 5 ml Carpujects®; Generic; (Rx) C-II
- Injectable Preservative Free 0.05 mg/ml in 2, 5, 10, & 20 ml amps Sublimaze®(Taylor); (Rx) C-II
- Transdermal: 2.5 mg (10 cm²; 25 mcg/hr); 5 mg (20 cm²; 50 mcg/hr); 7.5 mg (30 cm²; 75 mcg/hr); 10 mg (40 cm²; 100 mcg/hr); DuraGesic®-25 (etc.), (Janssen); (Rx) C-II
- Fentanyl Transmucosal System: 100 mcg, 200 mcg, 300 mcg & 400 mcg lozenges; Fentanyl Oralet® (Abbott) (Rx) CII; 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg & 1600 mcg lozenge on a stick; Actiq® (Abbott) (Rx) CII

All fentanyl products are Class-II controlled substances.

**FLUNIXIN MEGLUMINE**

**PRESCRIBER HIGHLIGHTS**
- Veterinary-only non-steroidal antiinflammatory agent used in a variety of species
- Contraindications: History of hypersensitivity.
- Caution in pts. w/preexisting GI ulcers, renal, hepatic or hematologic diseases. In horses w/colic may mask the behavioral and cardiopulmonary signs associated with endotoxemia or intestinal devitalization
- Because of adverse effects in dogs and cats, most recommend using one dose only.
- If first dose is ineffective for pain control, subsequent doses unlikely to be of benefit
- Adverse Effects: Horses and cattle: Rare anaphylaxis (esp. after rapid IV administration). IM injections may cause pain/swelling. GI distress/ulceration likely in dogs if used chronically.
- Drug Interactions

**CHEMISTRY**
Flunixin meglumine, a nonsteroidal anti-inflammatory agent that is a highly substituted derivative of nicotinic acid, is unique structurally when compared to other NSAIDs. The chemical name for flunixin is 3-pyridine-carboxylic acid.

**STORAGE/StABILITY/COMPATIBILITY**
All flunixin products should be stored between 2-30°C (36-86°F). It has been recommended that flunixin meglumine injection not be mixed with other drugs because of unknown compatibilities.

**PHARMACOLOGY**
Flunixin is a very potent inhibitor of cyclooxygenase and like other NSAIDs, it exhibits analgesic, anti-inflamatory and antipyretic activity. Flunixin does not appreciably alter GI motility in horses and may improve hemodynamics in animals with septic shock.

**PHARMACOKINETICS**
In the horse, flunixin is rapidly absorbed following oral administration with an average bioavailability of 80% and peak serum levels in 30 minutes. The onset of action is generally within 2 hours; peak response
occurs between 12-16 hours and the duration of action lasts up to 36 hours. It is unknown how extensively flunixin is bound to plasma proteins or where it distributes in the body. It is unclear if the drug is extensively metabolized and exactly how the drug is removed from the body. Serum half-lives have been determined in horses ~1.6 hours, dogs ~3.7 hours; cattle ~8.1 hours.

Flunixin is detectable in equine urine for at least 48 hrs. after a dose.

**USES/INDICATIONS**

In the United States, flunixin meglumine is approved for use in horses and cattle. However, it is approved for use in dogs in other countries. The approved indications for its use in the horse are for the alleviation of inflammation and pain associated with musculoskeletal disorders and alleviation of visceral pain associated with colic in the horse. In cattle it is approved for the control of pyrexia associated with bovine respiratory disease and endotoxemia, and for the control of inflammation in endotoxemia.

Flunixin has been touted for many other indications in various species, including: Horses: foal diarrheas, shock, colitis, respiratory disease, post-race treatment, and pre- and post ophthalmic and general surgery; Dogs: disk problems, arthritis, heat stroke, diarrhea, shock, ophthalmic inflammatory conditions, pre- and post ophthalmic and general surgery, and treatment of parvovirus infection; Cattle: acute respiratory disease, acute coliform mastitis with endotoxic shock, pain (downer cow), and calf diarrheas; Swine: agalactia/hypogalactia, lameness, and piglet diarrhea. It should be noted that the evidence supporting some of these indications is equivocal and flunixin may not be appropriate for every case.

**CONTRAINDICATIONS/PRECAUTIONS**

The only contraindication the manufacturer lists for flunixin's use in horses is for patients with a history of hypersensitivity reactions to it. It is suggested, however, that flunixin be used cautiously in animals with preexisting GI ulcers, renal, hepatic or hematologic diseases. When using to treat colic, flunixin may mask the behavioral and cardiopulmonary signs associated with endotoxemia or intestinal devitalization and must be used with caution.

In cattle, the drug is contraindicated in animals who have shown prior hypersensitivity reactions to it and is not recommended to be used in breeding bulls (lack of reproductive safety data).

Although reports of teratogenicity, effects on breeding performance, or gestation length have not been noted, flunixin should be used cautiously in pregnant animals.

Flunixin is usually considered to be contraindicated in cats, but some clinicians may use it short term (see doses).

**ADVERSE EFFECTS/WARNINGS**

When used for pain, if the animal does not respond to an initial dose, it is unlikely additional doses will be effective and may result in increased chances for toxicity. In horses following IM injection, reports of localized swelling, induration, stiffness, and sweating have been reported. Do not inject intra-arterially as it may cause CNS stimulation (hysteria), ataxia, hyperventilation, and muscle weakness. Symptoms are transient and generally do not require any treatment. Flunixin appears to be a relatively safe agent for use in the horse, but the potential does exist for GI intolerance, hypoproteinemia, and hematologic abnormalities to occur. Flunixin is not to be used in horses intended for food.

In horses and cattle, rare anaphylactic-like reactions have been reported, primarily after rapid IV administration.

In dogs, GI distress is the most likely adverse reaction. Symptoms may include, vomiting, diarrhea, and ulceration with very high doses or chronic use. There have been anecdotal reports of flunixin causing renal shutdown in dogs when used at higher dosages pre-operatively.

**OVERDOSAGE**

No clinical case reports of flunixin overdoses were discovered. It is suggested that acute overdosage be handled by using established protocols of emptying the gut (if oral ingestion and practical or possible) and treating the patient supportively.
**Drug Interactions**

Drug/drug interactions have not been appreciably studied for flunixin, but if it follows other NSAIDs it should be used cautiously with highly protein bound drugs such as phenytoin, valproic acid, oral anticoagulants, other anti-inflammatory agents, salicylates, sulfonamides, and the sulfonylurea antidiabetic agents.

Additionally, use flunixin cautiously with warfarin, methotrexate, and aspirin or other ulcerogenic agents. Flunixin could theoretically reduce the saline and diuretic effects of furosemide. Use with caution in patients with severe cardiac failure.

**Doses**

**Dogs**

a) 0.5 - 2.2 mg/kg IM or IV one time only (Jenkins 1987)
b) As an antidiarrheal/antipyretic: 1 mg/kg IV (do not administer more than once in an animal that has received corticosteroids. (Tams 1999)
c) For ocular indications: 0.25 mg/kg IV once daily for no more than 5 days at a time. May also be used preoperatively by injecting IV 30 minutes before ocular surgery. May dilute 1:9 (flunixin: sterile water) in syringe to administer accurately to very small animals. (Wyman 1986)
d) For ocular disease: 0.5 mg/kg IV bid for 1-2 treatments;
   For acute gastric dilatation: 1 mg/kg IV once;
   For GI tract obstruction: 0.5 mg/kg IV once to twice daily for 3 treatments (Morgan 1988)
e) For surgical pain: 1 mg/kg IV, SC or IM initially once; 1 mg/kg subsequent daily doses
   For pyrexia: 0.25 mg/kg IV, SC or IM once, may be repeated in 12-24 hours if needed
   For ophtho procedures: 0.25 - 1 mg/kg IV, IM or SC once, may be repeated in 12-24 hours if needed (Johnson 1996)

**Cats**

As an antiinflammatory/analgesic:
   For surgical pain: 0.25 mg/kg SC once; once, may be repeated in 12-24 hours if needed
   For pyrexia: 0.25 mg/kg IV, SC or IM once, may be repeated in 12-24 hours if needed (Johnson 1996)

**Ferrets**

a) 0.5 - 2 mg/kg PO or IM one time daily (Williams 2000)

**Rabbits/Rodents/Pocket Pets**

a) **Rabbits**: 1.1 mg/kg SC, IM, IV q12-24h (Ivey and Morrisey 2000)
b) **Rabbits**: 1.1 mg/kg SC or IM q12h

**Rodents**: 2.5 mg/kg SC or IM q12h (Huerkamp 1995)

c) **Chinchillas**: 1 - 3 mg/kg SC q12h. **Guinea pigs**: 2.5 - 5 mg/kg SC q12h. **Gerbils, Mice, Rats, Hamsters**: 2.5 mg/kg SC q12-24h (Adamcak and Otten 2000)

**Cattle**

a) For labeled indications: 1.1 - 2.2 mg/kg (1 -2 mls per 100 lbs. BW) given slow IV either once a day as a single dose or divided into two doses q12h for up to 3 days. Avoid rapid IV administration. (Package Insert; Banamine® - Schering).
b) For treatment of radial nerve injury: 250 - 500 mg IV or IM bid, may need only one treatment; taper and discontinue usually after 2-3 days. (Rebhun 1986)
c) For aseptic lameness in cattle: 1.1 mg/kg, must be administered within 24 hrs after onset of symptoms to be effective. (Berg 1986)
d) 2.2 mg/kg then 1.1 mg/kg q8h IV (Jenkins 1987)
**Horses**

Note: ARCI UCGFS Class 4 Drug

a) Injectable: 1.1 mg/kg IV or IM once daily for up to 5 days. For colic cases, use IV route and may redose when necessary.

Oral Paste: 1.1 mg/kg PO (see markings on syringe-calibrated in 250 lb. weight increments) once daily. One syringe will treat a 1000 lb. horse for 3 days.

Do not exceed 5 days of consecutive therapy.

Oral Granules: 1.1 mg/kg PO once daily. One packet will treat 500lbs of body weight. May apply on feed. Do not exceed 5 consecutive days of therapy. (Package Insert - Schering Animal Health for Banamine®)

b) For pain associated with colic: 1.1 mg/kg IM or IV once or twice daily. For anti-inflammatory and antiendotoxic effects: 0.25 - 0.5 mg/kg IV q6-8h (Moore 1999)

c) 1.1 mg/kg IM or IV; duration of effect averages 4-36 hrs depending upon cause and severity of abdominal pain. (Muir 1987)

d) For adjunctive treatment of laminitis: 1.1 mg/kg IM, IV or PO twice daily (Brumbaugh, Lopez et al. 1999)

**Birds**

a) 1 - 10 mg/kg IM. May be indicated for pain, shock and trauma. True analgesic effects unknown in avian species, but has no detrimental respiratory effects. Vomiting and straining to defecate may occur after administration. (Wheeler 1993)

b) As an anti-inflammatory analgesic: 1 - 10 mg/kg IM once daily. Note: Renal disease and death occur occasionally in psittacines after repeated doses of flunixin. Use the lowest possible dose for the shortest duration of time. Recommend supplemental hydration. (Clyde and Paul-Murphy 2000)

**Monitoring Parameters**

1) Analgesic/anti-inflammatory/antipyretic effects
2) GI effects in dogs
3) CBC’s, occult blood in feces with chronic use in horses

**Client Information**

If injecting IM, do not inject into neck muscles.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times**

**Veterinary-Approved Products**

Flunixin is approved only for use in horses not intended for food; for beef cattle and non-lactating dairy cattle. Slaughter withdrawal time in cattle = 4 days at labeled doses.

Flunixin Meglumine for Injection 50 mg/ml; in 50 ml, 100 ml & 250 ml vials; Banamine® (Schering-Plough), Amtech Flunixin Meglumine Injection® (Phoenix Scientific), EquiLeve® (Vetus), Equi-Phar Equigesic® (Vedco), Flumeclumine® (Phoenix Pharmaceuticals), Flunixamine® (Fort Dodge), Flunixin Meglumine (Vet Tek), Flunixin Meglumine Injection (Butler), Flunixin Meglumine Solution (PPC), Suppressor® (RXV); (Rx)

Flunixin Meglumine Oral Paste 1500 mg/syringe; 30 gram syringe containing 1500 mg flunixin in boxes of 6; Banamine® Paste (Schering-Plough); (Rx)

Flunixin Meglumine Oral Granules 250 mg: 10 gram sachets, each sachet contains 250 mg flunixin in boxes of 50. 500 mg: 20 g sachets, each sachet contains 500 mg flunixin in boxes of 25; Banamine® Granules (Schering-Plough); (Rx)

Flunixin may also be known as Finadyne®.

**Human-Approved Products**

None
HALOTHANE

PRESCRIBER HIGHLIGHTS
- Classic inhalant general anesthetic; still used but largely supplanted by more modern agents
- Contraindications: History or predilection towards malignant hyperthermia; significant hepatotoxicity after previous exposure. Caution in pts. w/ hepatic function impairment, cardiac arrhythmias, increased CSF or head injury, myasthenia gravis, or pheochromocytoma
- Adverse Effects: dose related hypotension, malignant hyperthermia-stress syndrome, cardiac depression and dysrhythmias, hepatotoxicity
- May be teratogenic, use w/ caution in pregnancy
- Drug interactions

CHEMISTRY
An inhalant general anesthetic agent, halothane occurs as a colorless, nonflammable, heavy liquid. It has a characteristic odor resembling chloroform and sweet, burning taste. Halothane is slightly soluble in water and miscible with alcohol. At 20°C, halothane's specific gravity is 1.872-1.877 and vapor pressure is 243 mm Hg.

STORAGE/StABILITY/COMPATIBILITY
Store halothane below 40°C in a tight, light-resistant container. Halothane stability is maintained by the addition of thymol and ammonia. The thymol does not vaporize so it may accumulate in the vaporizer causing a yellow discoloration. Do not use discolored solutions. Discolored vaporizer and wick may be cleaned with diethyl ether (all ether must be removed before reuse).

In the presence of moisture, halothane vapor can react with aluminum, brass and lead (not copper). Rubber and some plastics are soluble in halothane leading to their rapid deterioration.

PHARMACOLOGY
While the precise mechanism that inhalent anesthetics exert their general anesthetic effect is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Some key pharmacologic effects noted with halothane include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression (pronounced in ruminants), hypotension, vasodilatation, and myocardial depression.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for halothane in various species: Dog = 0.76; Cat = 0.82; Horse = 0.88; Human = 0.76. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).

USES/INDICATIONS
Halothane remains a useful general anesthetic in veterinary medicine due to its relative safety, potency, controllability, non-flammability, and comparative low cost.

PHARMACOKINETICS
Halothane is rapidly absorbed through the lungs. About 12% of absorbed drug is metabolized by the liver to trifluoroacetic acid (only small amounts), chlorine and bromine radicals which are excreted in the urine. The bulk of the absorbed drug is re-excreted by the lungs and eliminated with expired air. Halothane is distributed into milk.

CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY
Halothane is contraindicated in patients with a history or predilection towards malignant hyperthermia or significant hepatotoxicity after previous halothane exposure (see Adverse Reactions below). It should be used with caution (benefits vs. risks) in patients with hepatic function impairment, cardiac arrhythmias, increased CSF or head injury, myasthenia gravis, or pheochromocytoma (cardiac arrhythmias due to catecholamines).

Some animal studies have shown that halothane may be teratogenic; use only when benefits outweigh potential risks.
ADVERSE EFFECTS/WARNINGS
Hypotension may occur and is considered to be dosage related. A malignant hyperthermia-stress syndrome has been reported in pigs, horses, dogs and cats. Halothane may cause cardiac depression and dysrhythmias. Halothane-induced hypotension may be treated by volume expansion and dobutamine. Lidocaine has been used to treat or prevent halothane-induced cardiac dysrhythmias.

In humans, jaundice and a postanesthetic fatal liver necrosis has been reported rarely. The incidence of this effect in veterinary species is not known. However, halothane should be considered contraindicated for future use if unexplained fever, jaundice or other symptoms associated with hepatotoxicity occur.

DRUG INTERACTIONS
Acetaminophen is not recommended to be used for post-operative analgesia in animals who have received halothane anesthesia.

Because halothane sensitizes the myocardium to the effects of sympathomimetics, especially catecholamines, severe ventricular arrhythmias may result. Drugs included are: dopamine, epinephrine, norepinephrine, ephedrine, metaraminol, etc. If these drugs are needed, they should be used with caution and in significantly reduced dosages with intensive monitoring.

Non-depolarizing neuromuscular blocking agents, systemic aminoglycosides, systemic lincomycins should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur.

Reportedly, d-tubocurarine may cause significant hypotension if used with halothane.

Concomitant administration of succinylcholine with inhalation anesthetics (halothane, cyclopropane, nitrous oxide, diethyl ether) may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia.

LABORATORY CONSIDERATIONS
Halothane may transiently increase values of liver function tests.

DOSES

Dogs/Cats
(Note: Concentrations are dependent upon fresh gas flow rate; the lower the flow rate, the higher the concentration required.)

a) 3% (induction); 0.5 - 1.5% (maintenance) (Papich 1992)

b) 0.5 - 3.5%, inhaled (Hubbell 1994)

Rabbits/Rodents/Pocket Pets

a) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: Using a non-rebreathing system: Induction: 2 - 4%, maintenance: 0.25 - 2% (Anderson 1994); (Adams and Otten 2000)

Horses

a) For draft horses: Following induction, the largest ET tube that will comfortably fit (20 - 40 mm) should be placed and cuff inflated. In an oxygen-enriched semi-closed large animal circle system 4-5% of halothane is administered initially and is reduced as indicated by physical monitoring of neural reflexes and cardiopulmonary parameters. The goal should be the lowest concentration inhalant anesthetic that provides adequate surgical anesthesia and restraint. Most draft horses can be maintained on 2.5 - 3% halothane. (See reference for more information on monitoring and use.) (Geiser 1992)

MONITORING PARAMETERS
1) Respiratory and ventilatory status; 2) Cardiac rate/rhythm; blood pressure (particularly with "at risk" patients); 3) Level of anesthesia
Veterinary-Approved Products
Halothane, USP (with thymol 0.01% and ammonia 0.00025%) in 250 ml bottles; (Halocarbon);(Rx)

Human-Approved Products
Halothane in 250 ml bottles; Halothane® (Abbott) (Rx)

HYDROMORPHONE

Prescriber Highlights
- Injectable opiate sedative/restraining agent, analgesic and preanesthetic similar to oxymorphone
- Less expensive than oxymorphone on a per cc basis, but has shorter duration of action
- Contraindications: hypersensitivity to it, diarrhea caused by a toxic ingestion, prior to GI obstructive surgery (may cause vomiting). Caution: hypothyroidism, severe renal insufficiency (acute uremia), adrenocortical insufficiency, geriatric or severely debilitated patients, head injuries or increased intracranial pressure and acute abdominal conditions (e.g., colic). Extreme caution: respiratory disease or acute respiratory dysfunction.
- Adverse Effects: CNS depression, respiratory depression and bradycardia. Decreased GI motility with resultant constipation possible. Cats (high dosages): ataxia, hyperesthesia and behavioral changes (without concomitant tranquilization).
- Drug-drug; drug-lab interactions
- C-II controlled substance

Chemistry
A semi-synthetic phenanthrene-derivative opiate related to morphine, hydromorphone HCl occurs as white, fine, crystalline powder. It is freely soluble in water. The commercial injection has a pH of 4 - 5.5.

Storage/Stability/Compatibility
The injection should be stored at room temperature and protected from light. A slight yellowish tint to the solution may occur, but does not indicate loss of potency. The injection is reportedly stable for at least 24 hours when mixed with commonly used IV fluids if protected from light. Sodium bicarbonate or thiopental sodium are reportedly physically incompatible with hydromorphone injection.

Hydromorphone tablets should be stored at room temperature, in tight, light resistant containers. The suppositories should be kept in the refrigerator.

Pharmacology
Receptors for opiate analgesics are found in high concentrations in the limbic system, spinal cord, thalamus, hypothalamus, striatum, and midbrain. They are also found in tissues such as the gastrointestinal tract, urinary tract, and in other smooth muscle.

Opiate receptors are further broken down into five main sub-groups. Mu receptors are found primarily in the pain regulating areas of the brain. They are thought to contribute to the analgesia, euphoria, respiratory depression, physical dependence, miosis, and hypothermic actions of opiates. Kappa receptors are located primarily in the deep layers of the cerebral cortex and spinal cord. They are responsible for analgesia, sedation and miosis. Sigma receptors are thought to be responsible for the dysphoric effects (struggling, whining), hallucinations, respiratory and cardiac stimulation, and mydriatic effects of opiates. Delta receptors, located in the limbic areas of the CNS and epsilon receptors have also been described, but their actions have not been well explained at this time.

The morphine-like agonists (morphine, meperidine, oxymorphone, hydromorphone) have primary activity at the mu receptors, with some activity possible at the delta receptor. The primary pharmacologic effects of these agents include: analgesia, antitussive activity, respiratory depression, sedation, emesis, physical dependence, and intestinal effects (constipation/defecation). Secondary pharmacologic effects include: CNS: euphoria, sedation, & confusion. Cardiovascular: bradycardia due to central vagal stimulation, alpha-adrenergic receptors may be depressed resulting in peripheral vasodilation, decreased peripheral resistance, and baroreceptor inhibition. Orthostatic hypotension and syncope may occur. Urinary:
Increased bladder sphincter tone can induce urinary retention.

Various species may exhibit contradictory effects from these agents. For example, horses, cattle, swine, and cats may develop excitement after morphine injections and dogs may defecate after morphine. These effects are in contrast to the expected effects of sedation and constipation. Dogs and humans may develop miosis, while other species (especially cats) may develop mydriasis.

Hydromorphone is approximately 5 times more potent an analgesic on a weight basis when compared to morphine and approximately equal in potency to oxymorphone. At the usual doses employed, hydromorphone alone has good sedative qualities in the dog. Respiratory depression can occur especially in debilitated, neonatal or geriatric patients. Bradycardia, as well as a slight decrease in cardiac contractility and blood pressure may also be seen. Like oxymorphone, hydromorphone does initially increase the respiratory rate (panting in dogs) while actual oxygenation may be decreased and blood CO₂ levels may increase by 10 mmHg or more. Gut motility is decreased with resultant increases in stomach emptying times. Unlike either morphine or meperidine, hydromorphone may only infrequently cause mild histamine release in the dog or cat after IV injection.

USES/INDICATIONS
Like oxymorphone, hydromorphone is used in dogs and cats as a sedative/restraining agent, analgesic and preanesthetic. It may also be useful in other species, but little data or experience is available. Because of expense and availability issues with oxymorphone, hydromorphone is rapidly replacing it in veterinary medicine.

PHARMACOKINETICS
Hydromorphone is absorbed when given by IV, IM, SC, and rectal routes. The onset of analgesic efficacy occurs within 15-30 minutes, depending on route of administration.

The drug is metabolized in the liver; primarily by glucuronidation. Because cats are deficient in this metabolic pathway, half-lives in cats are probably prolonged. The glucuronidated metabolite is excreted by the kidney.

CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY
All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison’s), and in geriatric or severely debilitated patients. Hydromorphone is contraindicated in patients hypersensitive to narcotic analgesics, and in patients taking monoamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Because it may cause vomiting, its use should be considered contraindicated as a preanesthetic med in animals with suspect gastric dilation, volvulus or intestinal obstruction.

Hydromorphone should be used with extreme caution in patients with head injuries, increased intracranial pressure and acute abdominal conditions (e.g., colic) as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (e.g., pulmonary edema secondary to smoke inhalation).

Hydromorphone can cause bradycardia and therefore should be used cautiously in patients with preexisting bradyarrhythmias.

Neonatal, debilitated or geriatric patients may be more susceptible to the effects of hydromorphone and may require lower dosages. Patients with severe hepatic disease may have prolonged duration of action of the drug. If used in cats at high dosages, the drug has been recommended to be given along with a tranquilizing agent, as hydromorphone can produce bizarre behavioral changes in this species. This also is true in cats for the other opiate agents, such as morphine.

Opiate analgesics are also contraindicated in patients who have been stung by the scorpion species Centruroides sculpturatus Ewing and C. gertschi Stahnke as it may potentiate these venoms.

ADVERSE EFFECTS/WARNINGS
Hydromorphone has a similar adverse effect profile to oxymorphone or morphine in dogs and cats. CNS depression may be greater than desired, particularly when treating moderate to severe pain. Dose related respiratory depression is possible, and more likely during general anesthesia. Panting (may occur more often than with oxymorphone) and cough suppression (may be of benefit) may occur. Secondary to enhanced vagal tone, hydromorphone can cause bradycardia. This apparently occurs on par with morphine.
or oxymorphone. Hydromorphone may cause histamine release, which is generally clinically insignificant, but may be significant in critically ill animals. Vomiting and defecation can occur after dosing. Use caution when used as a preanesthetic. Constipation is possible with chronic dosing.

**Overdosage/Acute Toxicity**

Massive overdoses may produce profound respiratory and/or CNS depression in most species. Other effects may include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, and animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of oxymorphone are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

In susceptible patients, moderate overdoses may require naloxone and supportive treatment as well.

**Drug Interactions**

Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with hydromorphone. Hydromorphone is contraindicated in human patients receiving monoamine oxidase (MAO) inhibitors (rarely used in veterinary medicine) for at least 14 days after receiving MAO inhibitors. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of hydromorphone while on these agents.

**Laboratory Considerations**

Plasma amylase and lipase values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**Doses**

**Dogs**

- a) For perioperative pain: 0.1 - 0.2 mg/kg IM, IV or SC q2-4 hours (Pascoe 2000)
- b) For cancer pain: 0.08 - 0.2 mg/kg IV, IM, or SC (Lester and Gaynor 2000)
- c) For moderate to severe pain: 0.08 - 0.3+ mg/kg IV, IM or SC q2-6 hours (Mathews 2000)
- d) As a premed prior to moderately painful procedures: 0.1 mg/kg; may be combined with acepromazine (0.02 - 0.05 mg/kg) in young, healthy patients.

As a sedative/restraint agent for fractious or aggressive dogs: 0.1 - 0.2 mg/kg mixed with acepromazine (0.05 mg/kg) IM. Maximal effect usually reached in about 15 minutes, but an additional wait of another 15 minutes may be necessary in some dogs.

As an alternate induction method (especially in critical patients): hydromorphone 0.05 - 0.2 mg/kg IV, slowly to effect followed by diazepam 0.02 mg/kg IV (do not mix two drugs together). Endotracheal intubation may be possible after administration, if not, delivery of an inhalant by face mask will give a greater depth of anesthesia. Positive pressure ventilation likely will be necessary. If bradycardia requires treatment, use either glycopyrrolate (0.01 - 0.02 mg/kg IV) or atropine (0.02 - 0.04 mg/kg IV). (Pettifer and Dyson 2000)

**Cats**

- a) For perioperative pain: 0.1 - 0.2 mg/kg IM or SC q2-4 hours (Pascoe 2000)
- b) For cancer pain: 0.08 - 0.2 mg/kg IV, IM, or SC (Lester and Gaynor 2000)
- c) For moderate to severe pain: 0.08 - 0.3+ mg/kg IV, IM or SC q2-6 hours (Mathews 2000)
- d) As a premed prior to moderately painful procedures: 0.1 mg/kg; may be combined with acepromazine (0.05 - 0.2 mg/kg) in young, healthy patients.

As an alternate induction method (especially in critical patients): hydromorphone 0.05 - 0.2 mg/kg IV, slowly to effect followed by diazepam 0.02 mg/kg IV (do not mix two drugs together). Endotracheal intubation may be possible after administration, if not, delivery of an inhalant by face mask will give a greater depth of anesthesia. Positive pressure ventilation likely will be necessary. If bradycardia requires treatment, use either glycopyrrolate (0.01 - 0.02 mg/kg IV) or atropine (0.02 - 0.04 mg/kg IV). (Pettifer and Dyson 2000)
**MONITORING PARAMETERS**
1) Respiratory rate/depth (pulse oximetry highly recommended); 2) CNS level of depression/excitation; 3) Blood pressure if possible and indicated (especially with IV use);
4) Cardiac rate; 5) Analgesic efficacy

**CLIENT INFORMATION**
When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**
None

**Human-Approved Products**
Hydromorphone HCl Parenteral Injection 1 mg/ml (1 ml amps), 2 mg/ml (1 ml amps, 20 ml vials), 4 mg/ml (1 ml amps) and 10 mg/ml (for IV infusion only); *Dilaudid*® (Knoll); Generic; (Rx), C-II
Also available are oral tablets (1, 2, 3, 4, & 8 mg), oral liquid (1 mg/ml) and rectal suppositories (3 mg).

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**ISOFURANE**

**PRESCRIBER HIGHLIGHTS**
- Inhalant general anesthetic
- Contraindications: history or predilection towards malignant hyperthermia. Caution with increased CSF or head injury, or myasthenia gravis.
- Adverse Effects: Dose related hypotension, respiratory depression, and GI effects (nausea, vomiting, ileus). Cardiodepression generally is minimal at doses causing surgical planes of anesthesia. Arrhythmias are rare.
- May be fetotoxic
- Drug interactions

**CHEMISTRY**
An inhalant general anesthetic agent, isoflurane occurs as a colorless, nonflammable, stable liquid. It has a characteristic mildly pungent musty, ethereal odor. At 20°C, isoflurane's specific gravity is 1.496 and vapor pressure is 238 mm Hg.

**STORAGE/StABILITY/COMPATIBILITY**
Isoflurane should be stored at room temperature; it is relatively unaffected by exposure to light, but should be stored in a tight, light-resistant container. Isoflurane does not attack aluminum, brass, tin, iron or copper.

**PHARMACOLOGY**
While the precise mechanism that inhalent anesthetics exert their general anesthetic effects is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Some key pharmacologic effects noted with isoflurane include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression, hypotension, vasodilatation, and myocardial depression (less so than with halothane) and muscular relaxation.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for isoflurane in various species: Dog = 1.5; Cat = 1.2; Horse = 1.31; Human = 1.2. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).
USES/INDICATIONS
Isoflurane is an inhalant anesthetic that has some distinct advantages over either halothane or methoxyflurane due to its lessened myocardial depressant and catecholamine sensitizing effects, and the ability to use it safely in patients with either hepatic or renal disease. Isoflurane's higher cost than either methoxyflurane or halothane is a disadvantage.

Horses may recover more rapidly than with halothane, but be more susceptible to anesthetic associated-myopathy.

PHARMACOKINETICS
Isoflurane is rapidly absorbed from the alveoli. It is rapidly distributed into the CNS and crosses the placenta. The vast majority of the drug is eliminated via the lungs; only about 0.17% is metabolized in liver and only very small amounts of inorganic fluoride is formed.

CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY
Isoflurane is contraindicated in patients with a history or predilection towards malignant hyperthermia. It should be used with caution (benefits vs. risks) in patients with increased CSF or head injury, or myasthenia gravis.

Some animal studies have indicated that isoflurane may be fetotoxic. Use during pregnancy with caution.

ADVERSE EFFECTS/WARNINGS
Hypotension (secondary to vasodilation, not cardiodepression) may occur and is considered to be dose related. Dose-dependent respiratory depression, and GI effects (nausea, vomiting, ileus) have been reported. While cardiodepression generally is minimal at doses causing surgical planes of anesthesia, it may occur. Arrhythmias have also rarely been reported.

DRUG INTERACTIONS
While isoflurane sensitizes the myocardium to the effects of sympathomimetics less so than halothane, arrhythmias may still result. Drugs included are: dopamine, epinephrine, norepinephrine, ephedrine, metaraminol, etc. Caution and monitoring is advised.

Non-depolarizing neuromuscular blocking agents, systemic aminoglycosides, systemic lincomycins should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur.

Concomitant administration of succinylcholine with inhalation anesthetics may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia as well.

DOSES
Dogs/Cats
(Note: Concentrations are dependent upon fresh gas flow rate; the lower the flow rate, the higher the concentration required.)

a) 5% induction; 1.5 - 2.5% maintenance (Papich 1992)
b) 0.5 - 3 %, inhaled (Hubbell 1994)

Rabbits/Rodents/Pocket Pets

a) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: Using a non-rebreathing system: Induction: 2 - 3%, maintenance: 0.25 - 2% (Anderson 1994); (Adamcak and Otten 2000)
Reptiles:

a) Give 5% isoflurane and oxygen in a clear plastic bag or induction chamber. Fill chamber with gas and seal. Induction time may take 30 - 60 minutes, but can be shortened to 15 - 30 minutes with increased depth of anesthesia if animal is injected with 10-20 mg/kg of ketamine (SC or IM). Patient should be kept warm by placing on a water blanket. Surgical anesthesia can be determined by the loss of righting reflex. After induction, use either a mask, ET tube, or leave head in chamber. Maintenance levels are 3-5% (if isoflurane used alone). If apnea occurs during or after anesthesia, discontinue gas anesthetic and apply gentle manual ventilation 2 - 4 times per minute with small doses of doxapram IV. Normal respiration generally resumes in 3-5 minutes. Righting reflex generally recovers in an hour, but animal may be tranquilized for 24 hours. (Gillespie 1994)

Birds

a) Small birds can be anesthetized safely in 15-30 seconds at 4% (Ludders 1992)

MONITORING PARAMETERS
1) Respiratory and ventilatory status; 2) Cardiac rate/rhythm; blood pressure (particularly with "at risk" patients; 3) Level of anesthesia

DOSEAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES

Veterinary-Approved Products
Isoflurane Inhalation Anesthetic, 99.9%/ml in 100 ml & 250 ml bottles; Approved for use in horses (those not intended for food) & dogs. Isoflo® (Abbott), Isoflurane, USP (Halocarbon., Phoenix Pharmaceutical), Iso-Thesia® (Vetus), (Rx)

Human-Approved Products
Isoflurane in 100 ml bottles; Isoflurane®(Abbott), Forane® (Anaquest); (Rx)

KETAMINE HCL

PRESCRIBER HIGHLIGHTS

- Dissociative general anesthetic
- Contraindications: prior hypersensitivity reactions; animals to be used for human consumption, alone for general anesthesia, increased CSF pressure/head trauma Relative contraindications: significant blood loss, malignant hyperthermia, increased intra-ocular pressure or open globe injuries; procedures involving the pharynx, larynx, or trachea. Caution: significant hypertension, heart failure, and arterial aneurysms, hepatic or renal insufficiency, seizure disorders.
- Adverse Effects: hypertension, hypersalivation, respiratory depression, hyperthermia, emesis, vocalization, erratic and prolonged recovery, dyspnea, spastic jerking movements, seizures, muscular tremors, hypertonicity, opisthotonos and cardiac arrest. Pain after IM injection may occur.
- Cat’s eyes remain open after ketamine; protect
- Minimize exposure to handling or loud noises during the recovery period; adequate monitoring must occur however.
- Drug interactions

CHEMISTRY
A congener of phencyclidine, ketamine HCl occurs as white, crystalline powder. It has a melting point of 258-261°C, a characteristic odor, and will precipitate as the free base at high pH. One gram is soluble in 5 ml of water, and 14 ml of alcohol. The pH of the commercially available injections are between 3.5-5.5.

STORAGE/STABILITY/COMPATIBILITY
Ketamine may be mixed with sterile water for injection, D₂W, and normal saline for diluent purposes. Ketamine is physically compatible with xylazine in the same syringe. Do not mix ketamine with barbiturates or diazepam in the same syringe or IV bag as precipitation may occur.
**PHARMACOLOGY**

Ketamine is a rapid-acting general anesthetic that also has significant analgesic activity and a lack of cardiopulmonary depressant effects. It is thought to induce both anesthesia and amnesia by functionally disrupting the CNS through over stimulating the CNS or inducing a cataleptic state. Ketamine inhibits GABA, and also may block serotonin, norepinephrine, and dopamine in the CNS. The thalamocortical system is depressed while the limbic system is activated. It induces anesthetic stages I & II, but not stage III. In cats, it causes a slight hypothermic effect as body temperatures decrease on average by 1.6°C after therapeutic doses.

Effects on muscle tone are described as being variable, but ketamine generally either causes no changes in muscle tone or increased tone. Ketamine does not abrogate the pinna reflexes, nor the photic, corneal, laryngeal or pharyngeal reflexes.

Ketamine's effects on the cardiovascular system include increased cardiac output, heart rate, mean aortic pressure, pulmonary artery pressure, and central venous pressure. Its effects on total peripheral resistance are described as being variable. Cardiovascular effects are secondary to increased sympathetic tone; ketamine has negative inotropic effects if the sympathetic system is blocked.

Ketamine does not cause significant respiratory depression at usual doses, but at higher doses it can cause respiratory rates to decrease. In humans with asthma, ketamine causes decreased airway resistance.

**USES/INDICATIONS**

Ketamine has been approved for use in humans, sub-human primates and cats, although it has been used in many other species (see dosage section). The approved indications for cats include, "for restraint, or as the sole anesthetic agent for diagnostic, or minor, brief, surgical procedures that do not require skeletal muscle relaxation.... and in subhuman primates for restraint." (Package Insert; Ketaset® - Bristol).

**PHARMACOKINETICS**

After IM injection in the cat, peak levels occur in approximately 10 minutes. Ketamine is distributed into all body tissues rapidly, with highest levels found in the brain, liver, lung, and fat. Plasma protein binding is approximately 50% in the horse, 53% in the dogs, and 37-53% in the cat.

The drug is metabolized in the liver principally by demethylation and hydroxylation and these metabolites along with unchanged ketamine are eliminated in the urine. Ketamine will induce hepatic microsomal enzymes, but there appears to be little clinical significance associated with this effect. The elimination half-life in the cat, calf, and horse is approximately 1 hour, in humans it is 2-3 hours. Like the thiobarbiturates, the redistribution of ketamine out of the CNS is more of a factor in determining duration of anesthesia than is the elimination half-life.

By increasing the dose, the duration of anesthesia will increase, but not the intensity.

**CONTRAINDICATIONS/PRECAUTIONS**

Ketamine is contraindicated in patients who have exhibited prior hypersensitivity reactions to it and in animals to be used for human consumption. Its use in patients with significant hypertension, heart failure, and arterial aneurysms could be hazardous. The manufacturer warns against its use in hepatic or renal insufficiency, but in humans with renal insufficiency the duration of action has been demonstrated not to be prolonged. Because ketamine does not give good muscle relaxation, it is contraindicated when used alone for major surgery.

Ketamine can cause increases in CSF pressure and it should not be used in cases with elevated pressures or when head trauma has occurred. Because of its supposed epileptogenic potential, it should generally not be used (unless very cautiously) in animals with preexisting seizure disorders. As myelography can induce seizures, ketamine should be used cautiously in animals undergoing this procedure.

Ketamine is considered to be relatively contraindicated when increased intra-ocular pressure or open globe injuries exist, and for procedures involving the pharynx, larynx, or trachea. Animals who have lost significant amounts of blood, may require significantly reduced ketamine dosages.

While ketamine has been used safely in humans with malignant hyperthermia, its use in animals susceptible to this is controversial. Hyperthyroid human patients (and those receiving exogenous thyroid replacement) may be susceptible to developing severe hypertension and tachycardia when given ketamine. The veterinary significance of this potential problem is unknown.
Cat’s eyes remain open after receiving ketamine, and should be protected from injury plus an ophthalmic lubricant (e.g., Lacri-Lube®) should be applied to prevent excessive drying of the cornea.

To minimize the incidences of emergence reactions, it is recommended to minimize exposure to handling or loud noises during the recovery period. The monitoring of vital signs should still be performed during the recovery phase, however.

Because ketamine can increase blood pressure, careful control of hemorrhaging post-surgery (e.g., declawing) should be accomplished. It is not essential to withhold food or water prior to surgery, but in elective procedures it is recommended to withhold food for 6 hours prior to surgery.

**ADVERSE EFFECTS/WARNINGS**

In approved species the following adverse reactions are listed by the manufacturer: "respiratory depression...following high doses, emesis, vocalization, erratic and prolonged recovery, dyspnea, spastic jerking movements, convulsions, muscular tremors, hypertonicity, opisthotonos and cardiac arrest. In the cat, myoclonic jerking and/or tonic/clonic convulsions can be controlled by ultrashort-acting barbiturates or acepromazine. These latter drugs must be given intravenously, cautiously, and slowly, to effect (approximately 1/6 to 1/4 the normal dose may be required)." (Package Insert; Ketaset® - Bristol)

Seizures have been reported to occur in up to 20% of cats that receive ketamine at therapeutic dosages. Diazepam is suggested to be been used for treatment if necessary. It has also been reported to rarely cause a variety of other CNS effects (mild CNS effects to blindness and death). Ketamine has been documented to cause hyperthermia in cats; low doses of acepromazine (0.01 - 0.02 mg/kg IV) may alleviate. Anecdotal reports of ketamine causing acute, CHF in cats with mild to moderate heart disease have been reported.

Pain after IM injection may occur.

To reduce the incidence of hypersalivation and other autonomic signs, atropine or glycopyrrolate is often administered.

**OVERDOSAGE**

Ketamine is considered to have a wide therapeutic index (approximately 5 times greater when compared to pentobarbital). When given in excessive doses or too rapidly, significant respiratory depression may occur. Treatment using mechanically assisted respiratory support is recommended versus the use of analeptic agents. In cats, yohimbine with 4-aminopyridine has been suggested to be used as a partial antagonist.

**DRUG INTERACTIONS**

Narcotics, barbiturates, or diazepam may prolong the recovery time after ketamine anesthesia. When used with halothane, ketamine recovery rates may be prolonged and the cardiac stimulatory effects of ketamine may be inhibited. Close monitoring of cardiac status is recommended when using ketamine with halothane. Chloramphenicol (parenteral) may prolong the anesthetic actions of ketamine.

Thyroid hormones when given concomitantly with ketamine have induced hypertension and tachycardia in humans. Beta-blockers (e.g., propranolol) may be of benefit in treating these effects.

Neuromuscular blockers (e.g., succinylcholine and tubocurarine) may cause enhanced or prolonged respiratory depression.
**DOSES**

**Dogs**

Note: Ketamine/xylazine has induced cardiac arrhythmias, pulmonary edema, and respiratory depression in dogs. This combination should be used with caution.

a) Diazepam 0.5 mg/kg IV, then ketamine 10 mg/kg IV to induce general anesthesia (Booth 1988a)

b) Midazolam 0.066 - 0.22 mg/kg IM or IV, then ketamine 6.6 - 11 mg/kg IM (Mandsager 1988)

c) Xylazine 2.2 mg/kg IM, in 10 minutes give ketamine 11 mg/kg IM. Dogs weighing more than 22.7 kg (50 lbs.) reduce dose of both drugs by approx. 25%. (Booth 1988a)

d) Atropine (0.044 mg/kg) IM, in 15 minutes give xylazine (1.1 mg/kg) IM, 5 minutes later give ketamine (22 mg/kg) IM (Booth 1988a)

**Cats**

Most clinicians recommend giving atropine or glycopyrrolate before use to decrease hypersalivation.

a) 11 mg/kg IM for restraint; 22 - 33 mg/kg for diagnostic or minor surgical procedures not requiring skeletal muscle relaxation. (Package Insert; Ketaset® - Bristol)

b) 2 - 4 mg/kg IV or 11 - 33 mg/kg IM (Davis 1985b)

c) Restraint: 0.1 ml (10 mg) IV.

Anesthesia: 22 - 33 mg/kg IM or 2.2 - 4.4 mg/kg IV (with atropine) (Morgan 1988)

d) Sedation, restraint: 6.6 - 11 mg/kg IM

Anesthetic:17.6 - 26.4 mg/kg IM

Induction (following sedation): 4.4 - 11 mg/kg IV (Mandsager 1988)

e) Restraint:11 mg/kg IM

Anesthesia:22 - 33 mg/kg IM; 2.2 - 4.4 mg/kg IV (Kirk 1986)

**Rabbits/Rodents/Pocket Pets**

For chemical restraint:

a) **Mice:** Alone: 50 -100 mg/kg IM or IP, 50 mg/kg IV. In combination with diazepam: Ketamine 200 mg/kg/Diazepam 5 mg/kg IM or IP. In combination with xylazine: Ketamine 100 mg/kg/Xylazine 5 - 15 mg/kg IM or IP. (Burke 1999)

b) **Rats:** Alone: 50 -100 mg/kg IM or IP, 40 - 50 mg/kg IV. In combination with diazepam: Ketamine 40 - 60 mg/kg/Diazepam 5 - 10 mg/kg IP. In combination with xylazine: Ketamine 40 - 75 mg/kg /Xylazine 5 - 12 mg/kg IM or IP. (Burke 1999)

c) **Hamsters/Gerbils:** 100 mg/kg IM. In combination with diazepam: Ketamine 50 mg/kg/Diazepam 5 mg/kg IM. In combination with xylazine: Not recommended. (Burke 1999)

d) **Guinea pig:** Alone: 10 - 30 mg/kg IM. In combination with diazepam: Ketamine 60 - 100 mg/kg/Diazepam 5 - 8 mg/kg IM. In combination with xylazine: Ketamine 85 mg/kg/Xylazine 12 -13 mg/kg IM. (Burke 1999)

e) **Rabbits:** Alone: 20 - 60 mg/kg IM or IV. In combination with diazepam: Ketamine 60 - 80 mg/kg/Diazepam 5 - 10 mg/kg IM. In combination with xylazine: Ketamine 10 mg/kg/Xylazine 3 mg/kg IV. (Burke 1999)

f) **Rabbits:** Alone: 20 - 50 mg/kg IM or 15 - 20 mg/kg IV.

In combination with diazepam for induction: Diazepam 5 - 10 mg/kg IM give ketamine 30 minutes after diazepam at 20 - 40 mg/kg IM or Diazepam 0.2 - 0.5 mg/kg and Ketamine 10 - 15 mg/kg (to effect) IV.

In combination with diazepam for anesthesia without inhalants: Diazepam 5 - 10 mg/kg IM plus ketamine 60 - 80 mg/kg IM 30 minutes later.

In combination with xylazine: Not recommended for pet rabbits. (Ivey and Morrisey 2000)
Ferrets
a) For injectable anesthesia: Butorphanol 0.1 mg/kg, Ketamine 5 mg/kg, medetomidine 80 mcg/kg. Combine in one syringe and give IM. May need to supplement with isoflurane (0.5 - 1.5%) for abdominal surgery. (Finkler 1999)

Cattle
a) Premedicate with atropine and xylazine, then ketamine 2.0 mg/kg IV bolus (Thurmon and Benson 1986)
b) After sedation, 2.2 mg/kg IV (Mandsager 1988)

Horses
Note: ARCI UCGFS Class 2 Drug
a) For field anesthesia: Sedate with xylazine (1.0 mg/kg IV; 2.0 mg/kg IM) given 5-10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either 1) Redose xylazine: up to half the original dose, 2) Add butorphanol (0.02 - 0.04 mg/kg IV). Butorphanol can be given with the original xylazine if you suspect that the horse will be difficult to tranquilize (e.g., high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5-10 minutes. 3) Diazepam (0.03 mg/kg IV). Mix the diazepam with the ketamine. This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5-10 minutes. 4) Guaiifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)
b) Initially give xylazine 1.1 mg/kg IV and wait for full sedative effect (4-8 minutes); then give ketamine 2.2 - 2.75 mg/kg IV only (the higher dose may be necessary for ponies, young "high-strung" Arabians, Hackneys, and Thoroughbreds) as a bolus. Do not administer to an "excited" horse. If surgery time requires additional anesthesia, 1/3-1/2 of the original xylazine/ketamine doses may be given IV. For procedures where better muscle relaxation is required, use guaiifenesin-thiobarbiturate. Do not disturb horse until fully recovered. (Thurmon and Benson 1987)
c) For foals and ponies: Add 500 mg ketamine and 250 mg xylazine to 500 ml of 5% guaiifenesin solution. For induction, give 1.1 ml/kg IV rapidly. Anesthesia may be maintained by constant IV infusion of 2-3 ml/kg/hr. Lower doses for foals, higher doses for ponies. (Thurmon and Benson 1987)
d) For induction of surgical colic patients: Use guaiifenesin to effect, than 1.6 - 2.2 mg/kg ketamine (Mandsager 1988)
e) 200 mg bolus (in a 454 kg horse) intra-operatively to reduce movement with light general anesthesia (Mandsager 1988)

Swine
a) Give atropine, then ketamine at 11 mg/kg IM. To prolong anesthesia and increase analgesia give additional ketamine 2 - 4 mg/kg IV. Local anesthetics injected at the surgical site (e.g., 2% lidocaine) may enhance analgesia. (Thurmon and Benson 1986)
b) Ketamine (22 mg/kg) combined with acepromazine (1.1 mg/kg) IM (Swindle 1985)
c) 4.4 mg/kg IM or IV after sedation (Mandsager 1988)

Sheep
a) Premedicate with atropine (0.22 mg/kg) and acepromazine (0.55 mg/kg; then ketamine 22 mg/kg IM. To extend anesthetic time, may give ketamine intermittently IV at 2 - 4 mg/kg. (Thurmon and Benson 1986)
b) 2 mg/kg IV for induction, then 4 ml/minute constant infusion of ketamine in a concentration of 2 mg/ml in D5W. (Thurmon and Benson 1986)
Goats

a) Give atropine 0.4 mg/kg, followed by xylazine 0.22 mg/kg IM 20-25 minutes later. Approximately 10 minutes after xylazine give ketamine 11 mg/kg IM. To extend anesthesia give ketamine 2 - 4 mg/kg IV (shorter extension) or 6 mg/kg (longer extension). (Thurmon and Benson 1986)

Reptiles

a) Medium to small land tortoises: Medetomidine 100 - 150 mcg/kg with ketamine 5 - 10 mg/kg IV or IM.
Freshwater Turtles: Medetomidine 150 - 300 mcg/kg with ketamine 10 - 20 mg/kg IV or IM
Giant land tortoises: 200 kg Aldabra tortoise: Medetomidine 40 mcg/kg with ketamine 4 mg/kg IV or IM. Smaller Aldabra tortoises: Medetomidine 40 - 80 mcg/kg with ketamine 4 - 8 mg/kg IV or IM. Wait 30-40 minutes for peak effect.
Iguanas: Medetomidine 100 - 150 mcg/kg with ketamine 5 - 10 mg/kg IV or IM.
Reversal of all dosages with atipamezole is 4-5 times the medetomidine dose. (Heard 1999)
b) 20 - 60 mg/kg IM (McConnell and Hughey 1987)

Sub-Human Primates

a) Doses vary with regard to individual species; refer to package insert for Ketaset®.

Birds

a) Birds weighing:
< 100 grams (canaries, finches, budgies):0.1 - 0.2 mg/gm IM
250 - 500 grams (parrots, pigeons):0.05 - 0.1 mg/gm IM
500 gms - 3 kg (chickens, owls, hawks):0.02 - 0.1 mg/gm IM
> 3 kg (ducks, geese, swans):0.02 - 0.05 mg/gm IM (Booth 1988a)
b) In combination with xylazine: Ketamine 10 - 30 mg/kg IM; Xylazine 2 - 6 mg/kg IM; birds less than 250 g require a higher dosage than birds weighing greater than 250 g. Xylazine is not recommended to be used in debilitated birds because of its cardiodepressant effects.
In combination with diazepam: Ketamine 10 - 50 mg/kg IM; Diazepam 0.5 - 2 mg/kg IM or IV; doses can be halved for IV use.
In combination with acepromazine: Ketamine 25 - 50 mg/kg IM; Acepromazine 0.5 - 1 mg/kg IM. (Wheler 1993)

MONITORING PARAMETERS

1) Level of anesthesia/analgesia
2) Respiratory function; cardiovascular status (rate, rhythm, BP if possible)
3) Monitor eyes to prevent drying or injury
4) Body temperature

CLIENT INFORMATION

Should only be administered by individuals familiar with its use.

Veterinary-Approved Products

Ketamine HCl for Injection 100 mg/ml in 10 ml vials; Amtech® Ketamine Hydrochloride Injection, USP (Phoenix Scientific) (C-III), Ketaflo® (Abbott) (CIII), Ketaject® (Phoenix Pharmaceutical) (Rx), Ketaset® (Fort Dodge) (CIII), Keta-sthetic® (RXV) (Rx), Ketaved® (Vedco) (Rx); Vetalar® (Fort Dodge) (CIII); VetaKet® (Lloyd) (CIII), Vetamine® (Schering-Plough) (Rx) Approved for use in cats and sub-human primates.

Human-Approved Products

Ketamine HCl for Injection 10 mg/ml in 20 ml vials; 50 mg/ml in 10 ml vials; 100 mg/ml in 5 ml vials; Ketalar® (Monarch); generic (Rx) (CIII)
**KEToprofen**

**Prescriber Highlights**
- Nonsteroidal antiinflammatory agent used in horses, cats and dogs
- Contraindications: hypersensitivity to ketoprofen. Cautions: GI ulceration or bleeding, hypoproteinemia, breeding animals (especially late in pregnancy), significant renal or hepatic impairment. May mask the signs and symptoms (inflammation, hyperpyrexia) of infection.
- Adverse Effects: Horses: Potentially, gastric mucosal damage and GI ulceration, renal crest necrosis, and mild hepatitis may occur. Dogs: vomiting, anorexia, and GI ulcers
- Do not administer intra-arterially and avoid SC injections
- Drug-drug; drug-lab interactions

**Chemistry**
A propionic acid derivative nonsteroidal anti-inflammatory agent (NSAID), ketoprofen occurs as an off white to white, fine to granular powder. It is practically insoluble in water, but freely soluble in alcohol at 20°C. Ketoprofen has a pKₐ of 5.9 in a 3:1 methanol:water solution. Ketoprofen has both an S enantiomer and R enantiomer. The commercial product contains a racemic mixture of both. The S (+) enantiomer has greater antiinflammatory potency than the R (-) form.

**Storage/Stability/Compatibility**
Ketoprofen oral capsules should be stored at room temperature in tight, light resistant containers. The veterinary injection should be stored at room temperature. Compatibility studies with injectable ketoprofen and other compounds have apparently not been published.

**Pharmacology**
Ketoprofen exhibits actions similar to that of other nonsteroidal antiinflammatory agents in that it possesses antipyretic, analgesic and antiinflammatory activity. Its purported mechanism of action is the inhibition of cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors (endoperoxides), thereby inhibiting the synthesis of prostaglandins in tissues. Ketoprofen purportedly has inhibitory activity on lipoxygenase, whereas flunixin reportedly does not at therapeutic doses. In vivo studies have not confirmed lipoxygenase activity in studied species.

The S (+) enantiomer is associated with anti-prostaglandin activity and toxicity and the R (-) form analgesia without the GI effects.

**Uses/Indications**
Ketoprofen is labeled for use in horses for the alleviation of inflammation and pain associated with musculoskeletal disorders. Like flunixin (and other NSAIDs), ketoprofen potentially has many other uses in a variety of species and conditions. There are approved dosage forms for dogs in cats in Europe and Canada. Some consider ketoprofen to be the NSAID of choice for use in cats.

**Pharmacokinetics**
In species studied (rats, dog, man), ketoprofen is rapidly and nearly completely absorbed after oral administration. The presence of food or milk decreases oral absorption. Oral absorption characteristics in horses was not located. It has been reported that when comparing IV vs. IM injections in horses, the areas under the curve are relatively equivalent.

While distribution characteristics are not well described, the drug does enter synovial fluid and is highly bound to plasma proteins (99% in humans, and approximately 93% in horses). In horses, the manufacturer reports that the onset of activity is within 2 hours and peak effects 12 hours post dose.

Ketoprofen is eliminated via the kidneys both as a conjugated metabolite and unchanged drug. The elimination half life in horses is approximately 1.5 hours.
CONTRAINDICATIONS/ PRECAUTIONS/ REPRODUCTIVE SAFETY
While the manufacturer states that there are no contraindications to the drug’s use (other than previous hypersensitivity to ketoprofen), it should be used only when the potential benefits outweigh the risks in cases where GI ulceration or bleeding is evident or in patients with significant renal or hepatic impairment.

Ketoprofen may mask the signs and symptoms (inflammation, hyperpyrexia) of infection. Because ketoprofen is highly protein bound, patients with hypoproteinemia may have increased levels of free drug, thereby increasing the risks for toxicity.

The manufacturer cautions against ketoprofen’s use in breeding animals, because effects on fertility, pregnancy or fetal health have not been established in horses. However, rat and mice studies have not demonstrated increased teratogenicity or embryotoxicity. Rabbits receiving twice the human dose exhibited increased embryotoxicity, but not teratogenicity. Because non-steroidal antiinflammatory agents inhibit prostaglandin synthesis, adversely affecting neonatal cardiovascular systems (premature closure of patent ductus), ketoprofen should not be used late in pregnancy. Studies in male rats demonstrated no changes in fertility.

It is presently unknown whether ketoprofen enters equine milk. Ketoprofen does enter canine milk.

ADVERSE EFFECTS/WARNINGS
Because ketoprofen is a relatively new agent, its adverse effect profile in horses has not been clearly elucidated. Preliminary studies and reports indicate that ketoprofen appears relatively safe to use in horses and may have a lower incidence of adverse effects than either phenylbutazone or flunixin. Potentially, gastric mucosal damage and GI ulceration, renal crest necrosis, and mild hepatitis may occur.

Do not administer intra-arterially and avoid SC injections. While not labeled for IM use in horses, it reportedly is effective and may only cause occasional inflammation at the injection site.

In dogs, ketoprofen may cause vomiting, anorexia, and GI ulcers.

OVERDOSAGE/ACUTE TOXICITY
Horses given ketoprofen at doses up to 11 mg/kg administered IV once daily for 15 days exhibited no signs of toxicity. Severe laminitis was observed in a horse given 33 mg/kg/day (15X over labeled dosage) for 5 days. Anorexia, depression, icterus, and abdominal swelling was noted in horses given 55 mg/kg/day (25X labeled dose) for 5 days. Upon necropsy, gastritis, nephritis and hepatitis were diagnosed in this group.

Humans have survived oral ingestions of up to 5 grams. The LD₅₀ in dogs after oral ingestion has been reported to be 2000 mg/kg. General drug removal and supportive measures have been recommended in cases of oral overdosage.

DRUG INTERACTIONS
Because ketoprofen is highly bound to plasma proteins, it can displace or be displaced by other highly protein bound drugs, including warfarin, phenylbutazone, etc. Because ketoprofen may inhibit platelet aggregation and also cause gastrointestinal ulceration, when used with other drugs that alter hemostasis (e.g., heparin, warfarin, etc.) and/or cause gastrointestinal erosion (e.g., aspirin, flunixin, phenylbutazone, corticosteroids, etc.), increased likelihood of bleeding or ulceration may occur.

Ketoprofen and probenecid are not recommended to be used together. Probenecid reduces renal clearance of ketoprofen and also reduces its protein binding; thereby increasing the risk of toxicity.

Ketoprofen may decrease the efficacy of furosemide.

NSAIDs (including ketoprofen) may potentially significantly reduce the excretion of methotrexate and cause toxicity.
LABORATORY CONSIDERATIONS
Ketoprofen may cause falsely elevated blood glucose values when using the glucose oxidase and peroxidase method using ABTS as a chromogen; falsely elevated serum bilirubin values when using DMSO as a reagent; falsely elevated serum iron concentrations using the Ramsey method, or falsely decreased serum iron concentrations when using bathophenanthroline disulfonate as a reagent.

DOSES

Dogs
As an antiinflammatory/analgesic:
   a) For surgical pain: 2 mg/kg IV, SC or IM initially once; 1 mg/kg subsequent daily doses
   b) 2 mg/kg IV one time (Hardie 2000)
   c) For osteoarthritis unresponsive to aspirin: 0.5 - 1 mg/kg PO twice daily with food; decrease the dose by 50% when giving to geriatric patients (Trepanier 1999)

Cats
As an antiinflammatory/analgesic:
   a) For surgical pain: 2 mg/kg SC initially once; 1 mg/kg subsequent daily doses
   b) 2 mg/kg IV one time (Hardie 2000)

Rabbits/Rodents/Pocket Pets
   a) Rabbits: For chronic pain/antiinflammatory: 1 mg/kg IM q12-24h (Ivey and Morrisey 2000)
     b) Rats: 5 mg/kg SC (Adamcak and Otten 2000)

Horses
   a) For labeled indications: 2.2 mg/kg (1 ml/100 lbs) IV once daily for up to 5 days. (Package insert - Ketofen®)
   b) As an adjunctive treatment for laminitis: 2.2 mg/kg IV once daily (Brumbaugh, Lopez et al. 1999)

Birds
As an antiinflammatory analgesic 2 mg/kg IM q8-24 hours (Clyde and Paul-Murphy 2000)

MONITORING PARAMETERS
1) Efficacy; 2) Adverse Effects (occasional liver or renal function tests are recommended with long term therapy)

Veterinary-Approved Products:
    Ketoprofen Injection 100 mg/ml in 50 ml and 100 ml multi-dose vials; Ketofen® (Fort Dodge); (Rx) Approved for use in horses not intended for food.
    In Canada, there are approved oral dosage forms (5, 10, 20 mg tablets) and an injectable form (10 mg/ml) for use in dogs and cats.

Human-Approved Products
    Ketoprofen Oral Capsules 25 mg, 50 mg, 75 mg; Orudis® (Wyeth-Ayerst), generic; (Rx)
    Ketoprofen 12.5 mg Tablets; Orudis KT® (Whitehall-Robins); (OTC)
    Ketoprofen Extended Release 100 mg, 150 mg, 200 mg Capsules; Oruvail® (Wyeth-Ayerst), Ketoprofen (Andrx); (Rx)
**LIDOCAINE HCl**

**PREScriBER HIGHLIGHTS**
- Local anesthetic and antiarrhythmic agent; may be useful to tx post-operative ileus in horses
- Contraindications: known hypersensitivity to the amide-class local anesthetics, severe degree of SA, AV or intraventricular heart block (if not being artificially paced), or Adams-Stokes syndrome.
- Caution: liver disease, congestive heart failure, shock, hypovolemia, severe respiratory depression, marked hypoxia, bradycardia or incomplete heart block having VPC's, unless the heart rate is first accelerated.
- Cats tend to be more sensitive to the CNS effects of lidocaine; use with caution.
- Patients susceptible to malignant hyperthermia should receive intensified monitoring.
- Adverse Effects: Most common adverse effects reported are dose related (serum level) and mild. CNS signs include drowsiness, depression, ataxia, muscle tremors, etc.; nausea and vomiting (usually transient). Adverse cardiac effects usually only at high plasma concentrations.
- If an IV bolus is given too rapidly, hypotension may occur.
- Be certain not to use the product which contains epinephrine intravenously.
- Drug interactions

**CHEMISTRY**
A potent local anesthetic and antiarrhythmic agent, lidocaine HCl occurs as a white, odorless, slightly bitter tasting, crystalline powder with a melting point between 74° - 79°C and a pKₐ of 7.86. It is very soluble in water and alcohol. The pH of the commercial injection is adjusted to 5 - 7, and the pH of the commercially available infusion in dextrose 5% is adjusted to 3.5 - 6.

Lidocaine is also known as lignocaine HCl.

**STORAGE/STABILITY/COMPATIBILITY**
Lidocaine for injection should be stored at temperatures less than 40°C and preferably between 15-30°C; avoid freezing.

Lidocaine is **physically compatible** with most commonly used IV infusion solutions, including D5W, lactated Ringer's, saline, and combinations of these. It is also reportedly **physically compatible** with: aminophylline, bretylium tosylate, calcium chloride/glucophage/glucoseinate, carbencillin disodium, chloramphenicol sodium succinate, chlorothiazide sodium, cimetidine HCl, dexamethasone sodium phosphate, digoxin, diphenhydramine HCl, dobutamine HCl, ephedrine sulfate, erythromycin lactobionate, glycopyrrolate, heparin sodium, hydrocortisone sodium succinate, hydroxyzine HCl, insulin (regular), mephenemperone sodium, metaraminol bitartrate, methicillin sodium, metoclopramide HCl, nitrofurantoin sodium, oxytetracycline HCl, penicillin G potassium, pentobarbital sodium, phenylephrine HCl, potassium chloride, procainamide HCl, prochlorperazine edisylate, promazine HCl, sodium bicarbonate, sodium lactate, tetracycline HCl, verapamil HCl, and vitamin B-complex w/C.

Lidocaine **may not be compatible** with dopamine, epinephrine, isoproterenol or norepinephrine as these require low pH's for stability. Lidocaine is reportedly physically incompatible when mixed with: ampicillin sodium, cefazolin sodium, methoxexidal sodium, or phenytoin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**PHARMACOLOGY**
Lidocaine is considered to be a class IB (membrane-stabilizing) antidysrhythmic agent. It is thought that lidocaine acts by combining with fast sodium channels when inactive which inhibits recovery after repolarization. Class IB agents demonstrate rapid rates of attachment and dissociation to sodium channels. At therapeutic levels, lidocaine causes phase 4 diastolic depolarization attenuation, decreased automaticity, and either a decrease or no change in membrane responsiveness and excitability. These effects will occur at serum levels that will not inhibit the automaticity of the SA node, and will have little effect on AV node conduction or His-Purkinje conduction.

Lidocaine apparently has some enhancing effects on intestinal motility in patients with postoperative ileus. The mechanism for this effect is not well understood, but probably involves more than just blocking increased sympathetic tone.
USES/INDICATIONS
Besides its use as a local and topical anesthetic agent, lidocaine is used to treat ventricular arrhythmias, principally ventricular tachycardia and ventricular premature complexes in all species. Cats tend to be rather sensitive to the drug and some clinicians feel that it should not be used in this species as an antiarrhythmic. Lidocaine may be useful to treat ileus postoperatively in horses.

PHARMACOKINETICS
Lidocaine is not effective orally as it has a high first-pass effect. If very high oral doses are given, toxic symptoms occur (due to active metabolites?) before therapeutic levels can be reached. Following a therapeutic IV bolus dose, the onset of action is generally within 2 minutes and has a duration of action of 10-20 minutes. If a constant infusion is begun without an initial IV bolus it may take up to an hour for therapeutic levels to be reached. IM injections may be given every 1.5 hours in the dog, but because monitoring and adjusting dosages are difficult, it should be reserved for cases where IV infusions are not possible.

After injection, the drug is rapidly redistributed from the plasma into highly perfused organs (kidney, liver, lungs, heart) and is distributed widely throughout body tissues. It has a high affinity for fat and adipose tissue and is bound to plasma proteins, primarily alpha1-acid glycoprotein. It has been reported that lidocaine binding to this protein is highly variable and concentration dependent in the dog and may be higher in dogs with inflammatory disease. Lidocaine is distributed into milk. The apparent volume of distribution (Vd) has been reported to be 4.5 L/kg in the dog.

Lidocaine is rapidly metabolized in the liver to active metabolites (MEGX and GX). The terminal half-life of lidocaine in humans is 1.5-2 hours and has been reported to be 0.9 hours in the dog. The half-lives of lidocaine and MEGX may be prolonged in patients with cardiac failure or hepatic disease. Less than 10% of a parenteral dose is excreted unchanged in the urine.

CONTRAINDICATIONS/PRECAUTIONS
Cats tend to be more sensitive to the CNS effects of lidocaine; use with caution. Lidocaine is contraindicated in patients with known hypersensitivity to the amide-class local anesthetics, a severe degree of SA, AV or intraventricular heart block (if not being artificially paced), or Adams-Stokes syndrome. The use of lidocaine in patients with Wolff-Parkinson-White (WPW) syndrome is controversial. Some manufacturers state its use is contraindicated, but several physicians have used the drug in people.

Lidocaine should be used with caution in patients with liver disease, congestive heart failure, shock, hypovolemia, severe respiratory depression, or marked hypoxia. It should be also be used with caution in patients with bradycardia or incomplete heart block having VPC’s, unless the heart rate is first accelerated. Patients susceptible to developing malignant hyperthermia should receive lidocaine with intensified monitoring.

ADVERSE EFFECTS/WARNINGS
At usual doses and if the serum level remains within the proposed therapeutic range (1 - 5 micrograms/ml), serious adverse reactions are quite rare. The most common adverse effects reported are dose related (serum level) and mild. CNS signs include drowsiness, depression, ataxia, muscle tremors, etc. Nausea and vomiting may occur, but are usually transient. Adverse cardiac effects generally only occur at high plasma concentrations and are usually associated with PR and QRS interval prolongation and QT interval shortening. Lidocaine may increase ventricular rates if used in patients with atrial fibrillation. If an IV bolus is given too rapidly, hypotension may occur.

Be certain not to use the product which contains epinephrine intravenously.

OVERDOSAGE
In dogs, if serum levels of >8 micrograms/ml are attained, toxicity may result. Symptoms may include ataxia, nystagmus, depression, seizures, bradycardia, hypotension and, at very high levels, circulatory collapse. Because lidocaine is rapidly metabolized, cessation of therapy or reduction in infusion rates with monitoring may be all that is required for minor symptoms. Seizures or excitement may be treated with diazepam, or a short or ultrashort acting barbiturate. Longer acting barbiturates (e.g., pentobarbital) should be avoided. Should circulatory depression occur, treat with fluids, pressor agents and if necessary, begin CPR.

DRUG INTERACTIONS
Lidocaine levels or effects may be increased by concomitant administration of cimetidine or propranolol.
Other antiarrhythmics such as procainamide, quinidine, propranolol, phenytoin administered with lidocaine may cause additive or antagonistic cardiac effects and toxicity may be enhanced. Phenytoin when given IV with lidocaine may cause increased cardiac depression.

Large doses of lidocaine may prolong succinylcholine-induced apnea.

**LABORATORY INTERACTIONS**

Lidocaine may cause increased creatine kinase levels (CK).

**DOSES**

**Dogs**

a) Initial bolus of 2 mg/kg slowly IV, up to 8 mg/kg; or rapid IV infusion of 0.8 mg/kg/minute, if effective, then give constant rate infusion of 25 - 80 mcg/kg/minute (0.025 - 0.08 mg/kg/minute) (Ware 2000)

b) For rapid conversion of life-threatening, incessant, unstable ventricular tachycardia: Initial IV bolus of 1-2 mg/kg preferably over 30 seconds to judge response, higher doses may be required but rarely need to give 4 mg/kg. Once effectiveness determined, begin constant rate infusion at 25 - 80 mcg/kg/minute. Adjust dose to attain efficacy but without side effects. To prevent adverse effects total dose should not exceed 8 mg/kg over approximately one hour. Alternatively may give lidocaine at 4 mg/kg IM, but not if shock is present. Effects generally are seen in 10-15 minutes and persist for about 90 minutes. (Moise 2000)

**Cats**

Caution: Cats are reportedly very sensitive to the CNS effects of lidocaine, monitor carefully and treat seizures with diazepam.

a) Initially, IV bolus of 0.25 - 0.5 mg/kg given slowly; can repeat at 0.15 - 0.25 mg/kg in 5-20 minutes; if effective, 10 - 20 mcg/kg/minute (0.01 - 0.02 mg/kg/min) as a constant rate IV infusion. (Ware 2000)

**Horses**

For ventricular tachyarrhythmias:

a) Initially IV bolus of 1 - 1.5 mg/kg. Will generally distinguish between ventricular tachyarrhythmias (effective) and supraventricular tachyarrhythmias (no effect). To maintain effect, a constant IV infusion will be required. (Hilwig 1987)

b) 0.25 - 0.5 mg/kg IV (slowly) every 5-10 minutes up to a total dose of 1.5 mg/kg (Mogg 1999)

For postoperative ileus:

a) Initially, IV bolus of 1.3 mg/kg followed by a IV infusion of 0.05 mg/kg/minute for 24 hours. (Malone, Turner et al. 1999)

**MONITORING PARAMETERS**

1) ECG; 2) Symptoms of toxicity (see Adverse Effects and Overdosage); 3) If available and indicated, serum levels may be monitored. Therapeutic levels are considered to range from 1 - 6 micrograms/ml.

**CLIENT INFORMATION**

This drug should only be used by professionals familiar with its use and in a setting where adequate patient monitoring can be performed.

**DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

Lidocaine is approved for use in veterinary medicine (dogs, cats, horses, and cattle) as an injectable anesthetic, but it is not approved for use as an antiarrhythmic agent. Information regarding its use in food-producing species is conflicting. It is a prescription (Rx) drug.
Lidocaine HCl for Injection
1% (10 mg/ml) in 5 ml (50 mg) and 10 ml (100 mg) syringes
2% (20 mg/ml) in 5 ml single use vials and syringes (preservative free)
2% (20 mg/ml) in 100 ml multi-use vials; Veterinary (contains preservatives)

To prepare IV infusion solution using the veterinary 2% solution add 1 gram (50 ml of 2% solution to 1 liter of D5W or other compatible solution, this will give an approximate concentration of 1 mg/ml (1000 micrograms/ml). When using a mini-drip (60 drops/ml) IV set, each drop will contain approximately 17 micrograms. In small dogs and cats, a less concentrated solution may be used for greater dosage accuracy. When preparing solution be certain that you are not using the lidocaine product that also contains epinephrine.

Lidocaine (human approved) is also available in 4%, 10%, and 20% preservative free solutions for IV admixture, for direct IM administration, and premixed with D5W for IV infusion in concentrations of 2 mg/ml, 4 mg/ml, and 5 mg/ml.

Also known as lignocaine HCl. A common trade name is Xylocaine® (Astra).

Meloxicam

**Prescriber Highlights**
- NSAID used in dogs and cats (not available in USA at time of writing); COX-2 preferential
- Available in Canada/Europe as both an injectable and oral product
- GI adverse effects are less likely, but can occur
- Thus far has not shown hepatotoxicity or renal toxicity
- Drug-drug interactions

**Chemistry**
A COX-2 receptor preferential NSAID, meloxicam occurs as a pale yellow powder. It is in the oxicam class, related to piroxicam.

**Storage/Stability/Compatibility**
Unless otherwise labeled, store the injection and oral liquid at room temperature.

**Pharmacology**
Meloxicam has antiinflammatory, analgesic and antipyretic activity similar to other NSAIDs. Like other NSAIDs, meloxicam exhibits analgesic, anti-inflammatory, and antipyretic activity probably through its inhibition of cyclooxygenase, phospholipase A2, and inhibition of prostaglandin synthesis. It is considered to be COX-2 preferential (not COX-2 specific) as at higher dosages its COX-2 specificity is diminished.

Acute dosing studies in dogs have not demonstrated any untoward renal or hepatic toxicity.

**Uses/Indications**
Meloxicam is principally used for the symptomatic treatment of osteoarthritis in dogs. Short-term (single dose) use and pulse dosing in cats is also being investigated, but much less information on the use of this drug in cats is available.

**Pharmacokinetics**
In dogs, meloxicam is well absorbed after oral administration. Food does not alter absorption. Peak blood levels occur in about 7-8 hours after administration. The volume of distribution in dogs is 0.3 l/kg and about 97% is bound to plasma proteins. Meloxicam is extensively biotransformed to several different metabolites in the liver; none of these appear to have pharmacologic activity.

The majority of these (and unchanged drug) are eliminated in the feces. A significant amount of enterohepatic recirculation occurs. Elimination half-lives are species specific. The elimination half-life in dogs averages 24 hours (range: 12-36 hours). Other species: pigs: 4 hours; horses: 3 hours; cattle: 13 hours.
CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY

The European label states that meloxicam is contraindicated in dogs hypersensitive to it, with active GI ulceration or bleeding, impaired hepatic, cardiac or renal function and hemorrhagic disorders. The human label states that no dosage adjustment is necessary in patients with mild to moderate hepatic or renal impairment. Use extreme caution in dehydrated, hypovolemic or hypotensive animals as there is a potential increased risk of renal toxicity developing.

Not recommended for use in pregnant or lactating animals or in animals less than 6 weeks old.

ADVERSE EFFECTS/WARNINGS

Experience in Europe and Canada has demonstrated a relatively safe adverse effect profile for meloxicam in dogs. GI distress is the most commonly reported adverse effect, but apparently only occurs occasionally and is usually transient. Renal toxicity appears to be quite low. Very rarely, serious effects (including death) have been reported. It is unknown if the hepatotoxicity seen with some other NSAIDs used in dogs occurs with meloxicam.

OVERDOSAGE/ACUTE TOXICITY

No specific information located. Suggest to treat symptomatically and supportively.

DRUG INTERACTIONS

Because meloxicam is highly bound to plasma proteins, it can displace or be displaced by other highly protein bound drugs, including warfarin, phenylbutazone, etc.

Because meloxicam may inhibit platelet aggregation and also cause gastrointestinal ulceration; if used with other drugs that alter hemostasis (e.g., heparin, warfarin, etc.) and/or cause gastrointestinal erosion (e.g., aspirin, flunixin, phenylbutazone, corticosteroids, etc.), increased likelihood of bleeding or ulceration may occur.

Meloxicam may antagonize the antihypertensive effects of ACE inhibitors.

DOSES

Dogs
For osteoarthritis, analgesia, inflammatory conditions:
   a) 0.2 mg/kg PO initially, followed by 0.1 mg/kg PO (in food) once daily. (McLaughlin 2000)
   b) For surgical pain: 0.2 mg/kg (or less) IV or SC once; 0.1 mg/kg (or less) IV, SC, PO repeat every 24 hours.
      For chronic pain: 0.2 mg/kg (or less) PO once; 0.1 mg/kg (or less) PO repeat every 24 hours. (Mathews 2000)

Cats
For osteoarthritis, analgesia, inflammatory conditions:
   a) 0.2 mg/kg PO initially, followed by 0.1 mg/kg PO (in food) once daily for 2 days and then 0.025 mg/kg 2-3 times a week. (McLaughlin 2000)
   b) 0.1 mg/kg PO once daily (limit to 4 days use); 0.3 mg/kg IV or SC (one time use only) (Hardie 1997)
   c) For surgical pain: 0.2 mg/kg (or less) PO or SC once; 0.1 mg/kg (or less) SC, PO daily for 3-4 days.
      For chronic pain: 0.2 mg/kg (or less) PO, SC once; 0.1 mg/kg (or less) PO for 3-4 days; 0.025 mg/kg PO (0.1 mg maximum dose per cat) 2-3 times weekly. (Mathews 2000)

MONITORING PARAMETERS
1) Clinical efficacy 2) Adverse effects

CLIENT INFORMATION

Carefully measure dose (oral liquid); shake well before using. Mix oral liquid with food. If animal develops adverse effects contact the veterinarian.

DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHholding TIMES
Veterinary-Approved Products
None in the USA at time of writing. Meloxicam is available in Canada and Europe in both an oral liquid (1.5 mg/ml) and injectable form (5 mg/ml). Trade name is Metacam®.

Human-Approved Products
Meloxicam Oral Tablets 7.5 mg, 15 mg; Mobic® (Boehringer Ingelheim); (Rx)
In Canada, Mobicox® (Boehringer Ingelheim); (Rx)

Midazolam HCl

Prescriber Highlights
- Injectable benzodiazepine generally used primarily as a pre-op med
- Contraindications: hypersensitivity to benzodiazepines, or acute narrow-angle glaucoma. Caution: hepatic or renal disease and in debilitated or geriatric patients and those in coma, shock or having significant respiratory depression.
- Adverse Effects: Potential for respiratory depression of most concern
  44 Avoid intra-carotid injection
- Drug interactions

C-++ *HEMISTRY
An imidazobenzodiazepine, midazolam occurs as a white to light yellow crystalline powder with a pKₐ of 6.15. Midazolam HCl’s aqueous solubility is pH dependent. At 25°C and a pH of 3.4, 10.3 mg are soluble in 1 ml of water. The pH of the commercially prepared injection is approximately 3.

Storage/Stability/Compatibility
It is recommended to store midazolam injection at room temperature (15°-30°C) and protect from light. After being frozen for 3 days and allowed to thaw at room temperature, the injectable product was physically stable. Midazolam is stable at a pH from 3-3.6.

Midazolam is reportedly physically compatible when mixed with the following products: D₅W, normal saline, lactated Ringer’s, atropine sulfate, fentanyl citrate, glycopyrrolate, hydroxyzine HCl, ketamine HCl, meperidine HCl, morphine sulfate, nalbuphine HCl, promethazine HCl, sufentanil citrate, and scopolamine HBr. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

Pharmacology
Midazolam exhibits similar pharmacologic actions as other benzodiazepines (refer to the diazepam monograph for more information). Its unique solubility characteristics (water soluble injection but lipid soluble at body pH) give it a very rapid onset of action after injection.

Uses/Indications
In humans, midazolam has been suggested to be used as a premedicant before surgery, and when combined with potent analgesic/anesthetic drugs (e.g., ketamine or fentanyl), as a conscious sedative. In humans, midazolam reduces the incidences of "dreamlike" emergence reactions and increases in blood pressure and cardiac rate that ketamine causes.

When compared to the thiobarbiturate induction agents (e.g., thiamylal, thiopental), midazolam has less cardiopulmonary depressant effects, is water soluble, can be mixed with several other agents, and does not tend to accumulate in the body after repeated doses.

There is much interest in using the drug alone as an induction agent. Several veterinary anesthesiologists are studying the clinical applications of this agent in veterinary medicine and additional information regarding its use should be forthcoming.
PHARMACOKINETICS

Following IM injection, midazolam is rapidly and nearly completely (91%) absorbed. Although no oral products are being marketed, midazolam is well absorbed after oral administration, but because of a rapid first-pass effect, bioavailabilities suffer (31-72%). The onset of action following IV administration is very rapid due to the high lipophilicity of the agent. In humans, the loss of the lash reflex or counting occurs within 30-97 seconds of administration.

The drug is highly protein bound (94-97%) and rapidly crosses the blood-brain barrier. Because only unbound drug will cross into the CNS, changes in plasma protein concentrations and resultant protein binding may significantly alter the response to a given dose.

Midazolam is metabolized in the liver, principally by microsomal oxidation. An active metabolite (alpha-hydroxymidazolam) is formed, but because of its very short half-life and lower pharmacologic activity, it probably has negligible clinical effects. The serum half-life and duration of activity of midazolam in humans is considerably shorter than that of diazepam. Elimination half-lives measured in humans average approximately 2 hours (vs. approx. 30 hrs for diazepam).

CONTRAINDICATIONS/PRECAUTIONS

The manufacturer lists the following contraindications for use in humans: hypersensitivity to benzodiazepines, or acute narrow-angle glaucoma. Additionally, intra-carotid artery injections must be avoided.

Use cautiously in patients with hepatic or renal disease and in debilitated or geriatric patients. Patients with congestive heart failure may eliminate the drug more slowly. The drug should be administered to patients in coma, shock or having significant respiratory depression very cautiously.

Although midazolam has not been demonstrated to cause fetal abnormalities, in humans other benzodiazepines have been implicated in causing congenital abnormalities if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feeding, hyperbilirubinemia, hypotonia, etc. Withdrawal symptoms have occurred in infants whose mothers chronically took benzodiazepines during pregnancy. The veterinary significance of these effects is unclear, but the use of these agents during the first trimester of pregnancy should only occur when the benefits clearly outweigh the risks associated with their use. It is unknown if midazolam is distributed into milk, but other benzodiazepines and their metabolites are distributed into milk and may cause CNS effects in nursing neonates.

ADVERSE EFFECTS/WARNINGS

Few adverse effects have been reported in human patients receiving midazolam. Most frequently effects on respiratory rate, cardiac rate and blood pressure have been reported. Respiratory depression has been reported in patients who have received narcotics or have COPD. The following adverse effects have been reported in more than 1%, but less than 5% of patients receiving midazolam: pain on injection, local irritation, headache, nausea, vomiting, and hiccups.

The principle concern in veterinary patients is the possibility of respiratory depression occurring.

OVERDOSAGE

Very limited information is currently available. The IV LD₅₀ in mice has been reported to be 86 mg/kg. It is suggested that accidental overdoses be managed in a supportive manner, similar to diazepam.

DRUG INTERACTIONS

Use with barbiturates or other CNS depressants may increase the risk of respiratory depression occurring. Narcotics (including Innovar®) may increase the hypnotic effects of midazolam and hypotension has been reported when used with meperidine. Midazolam may decrease the dosages required for inhalation anesthetics or thiopental.
Doses

Dogs
As a preoperative agent: 0.066 - 0.22 mg/kg IM or IV (Mandsager 1988)

Cats
As a preoperative agent: 0.066 - 0.22 mg/kg IM or IV (Mandsager 1988)

Rabbits/Rodents/Pocket Pets:

a) Rabbits: As a tranquilizer (to increase relaxation of lightly anesthetized animals and permit ET intubation): 1 mg/kg IV prn (Huerkamp 1995)
b) Rabbits: 1 - 2 mg/kg IM IV. (Ivey and Morrisey 2000)
c) Hamsters, Gerbils, Mice, Rats, Guinea pigs, Chinchillas: 1 - 2 mg/kg IM (Adamcak and Otten 2000)
d) Rodents: 5 mg/kg IV (in combination with fentanyl/droperidol or fentanyl-fluanisone for neuroleptanesthesia) (Huerkamp 1995)

Horses
As a preoperative agent: 0.011 - 0.0.44 mg/kg IV (Mandsager 1988)

Birds
For adjunctive use (with an analgesic) for pain control: 1 - 2 mg/kg IM or IV (Clyde and Paul-Murphy 2000)

Monitoring Parameters
1) Level of sedation
2) Respiratory and cardiac signs

Client Information
This agent should be used in an inpatient setting only or with direct professional supervision where cardiorespiratory support services are available.

Human-Approved Products
Midazolam HCl for Injection 1 mg/ml in 2, 5, & 10 ml vials; 5 mg/ml in 1, 2, 5, & 10 ml vials; 2 ml syringes; Versed® (Roche); (Rx) (C-IV)
Midazolam HCl Syrup: 2 mg/ml in 118 ml bottles. Versed® (Roche) (C-IV)
Midazolam is a Class-IV controlled substance.

Morphine Sulfate

Prescriber Highlights
- Classic opiate analgesic
- Contraindications: hypersensitive to it, diarrhea caused by a toxic ingestion. Caution: hypothyroidism, severe renal insufficiency (acute uremia), adrenocortical insufficiency, geriatric or severely debilitated patients, head injuries or increased intracranial pressure and acute abdominal conditions (e.g., colic). Extreme caution: respiratory disease or from acute respiratory dysfunction.
- Adverse Effects: histamine release, respiratory depression, bronchoconstriction, CNS depression, GI Gastrointestinal effects may include: (nausea, vomiting, and decreased intestinal peristalsis), defecation (dogs), physical dependence (chronic use), hyperthermia (cattle, goats, horses and cats), hypothermia (dogs, rabbits).
- Drug-drug; drug-lab interactions
- C-II controlled substance
CHEMISTRY
The sulfate salt of a natural (derived from opium) occurring opiate analgesic, morphine sulfate occurs as white, odorless, crystals. Solubility: 1 g in 16 ml of water (62.5 mg/ml), 570 ml (1.75 mg/ml) of alcohol. Insoluble in chloroform or ether. The pH of morphine sulfate injection ranges from 2.5-6.

STORAGE/STABILITY/COMPATIBILITY
Morphine gradually darkens in color when exposed to light; protect from prolonged exposure to bright light. Does not appear to adsorb to plastic or PVC syringes, tubing or bags. Morphine sulfate has been shown to be physically compatible at a concentration of 16.2 mg/l with the following intravenous fluids: Dextrose 2.5%, 5%, 10% in water; Ringer's injection and Lactated Ringer's injection; Sodium Chloride 0.45% and 0.9% for injection. The following drugs have been shown to be physically incompatible when mixed with morphine sulfate: aminophylline, chlorothiazide sodium, heparin sodium, meperidine, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sodium bicarbonate, and thiotepal sodium. Morphine sulfate has been demonstrated to be generally physically compatible when mixed with the following agents: Atropine sulfate, benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, diphenhydramine HCl, droperidol, fentanyl citrate, hydroxyzine HCl, metoclopramide, pentazocine lactate, promazine HCl, scopolamine HBr, and succinylcholine chloride.

PHARMACOLOGY
Morphine's CNS effects are irregular and are species specific. Cats, horses, sheep, goats, cattle and swine may exhibit stimulatory effects after morphine injection, while dogs, humans, and other primates exhibit CNS depression. Both dogs and cats are sensitive to the emetic effects of morphine, but significantly higher doses are required in cats before vomiting occurs. This effect is a result of a direct stimulation of the chemoreceptor trigger zone (CTZ). Other species (horses, ruminants and swine) do not respond to the emetic effects of morphine. Like meperidine, morphine can effect the release of histamine from mast cells.

Morphine is an effective centrally acting antitussive in dogs. Following morphine administration, hypothermia may be seen in dogs and rabbits, while hyperthermia may be seen in cattle, goats, horses, and cats. Morphine can cause miosis (pinpoint pupils) in humans, rabbits and dogs.

While morphine is considered to be a respiratory depressant, initially in dogs respirations are stimulated. Panting may ensue which may be a result of increased body temperature. Often however, body temperature may be reduced due to a resetting of the "body's thermostat". As CNS depression increases and the hyperthermia resolves, respirations can become depressed. Morphine at moderate to high doses can also cause bronchoconstriction in dogs.

The cardiovascular effects of morphine in dogs are in direct contrast to its effects on humans. In dogs, morphine causes coronary vasoconstriction with resultant increase in coronary vascular resistance, and a transient decrease in arterial pressure. Both bradycardias and tachycardias have also been reported in dogs. While morphine has been used for years as a sedative/analgesic in the treatment of myocardial infarction and congestive heart failure in people, its effects on dogs make it a less than optimal choice in canine patients with symptoms of cardiopulmonary failure. However, its use has been recommended by several clinicians in the initial treatment for cardiogenic edema in dogs.

The effects of morphine on the gastrointestinal (GI) tract consist primarily of a decrease in motility and secretions. The dog however, will immediately defecate following an injection of morphine and then exhibit the signs of decreased intestinal motility and ultimately constipation can result. Both biliary and gastric secretions are reduced following administration of morphine, but gastric secretion of HCl will later be compensated by increased (above normal) acid secretion.

Initially, morphine can induce micturition, but with higher doses (>2.4 mg/kg IV) urine secretion can be substantially reduced by an increase in anti-diuretic hormone (ADH) release. Morphine may also cause bladder hypertonia, which can lead to increased difficulty in urination.

PHARMACOKINETICS
Morphine is absorbed when given by IV, IM, SC, and rectal routes. Although absorbed when given orally, bioavailability is reduced, probably as a result of a high first-pass effect. Morphine concentrates in the kidney, liver, and lungs; lower levels are found in the CNS. Although at lower levels then in the parenchymatous tissues, the majority of free morphine is found in skeletal muscle. Morphine crosses the placenta and narcotized newborns can result if mothers are given the drug before giving birth.
These effects can be rapidly reversed with naloxone. Small amounts of morphine will also be distributed into the milk of nursing mothers.

The major route of elimination of morphine is by metabolism in the liver; primarily by glucuronidation. Because cats are deficient in this metabolic pathway, half-lives in cats are probably prolonged. The glucuronidated metabolite is excreted by the kidney.

In horses, the serum half-life of morphine has been reported to be 88 minutes after a dose of 0.1 mg/kg IV. At this dose the drug was detectable in the serum for 48 hours and in the urine for up to 6 days. The half-life in cats has been reported to be approximately 3 hours.

**USES/INDICATIONS**

Morphine is used for the treatment of acute pain in dogs, cats, horses, swine, sheep, and goats. It may also be used as a preanesthetic agent in dogs and swine. Additionally, it has been used as an antitussive, antidiarrheal, and as adjunctive therapy for some cardiac abnormalities (see doses) in dogs.

**CONTRAINDICATIONS/PRECAUTIONS**

All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison’s), and in geriatric or severely debilitated patients. Morphine is contraindicated in cases where the patient is hypersensitive to narcotic analgesics, and in patients taking monoamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Morphine should be used with extreme caution in patients with head injuries, increased intracranial pressure and acute abdominal conditions (e.g., colic) as it may obscure the diagnosis or clinical course of these conditions. Morphine may also increase intracranial pressure secondary to cerebral vasodilatation as a result of increased p\textsubscript{a}CO\textsubscript{2} stemming from respiratory depression. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (e.g., pulmonary edema secondary to smoke inhalation).

Because of its effects on vasopressin (ADH), morphine must be used cautiously in patients suffering from acute uremia. Urine flow has been reported to be decreased by as much as 90% in dogs given large doses of morphine.

Neonatal, debilitated or geriatric patients may be more susceptible to the effects of morphine and may require lower dosages. Patients with severe hepatic disease may have prolonged duration of action of the drug.

Opiate analgesics are contraindicated in patients who have been stung by the scorpion species *Centruroides sculpturatus* Ewing and *C. gertschi* Stahnke as they can potentiate these venoms.

**ADVERSE EFFECTS/WARNINGS**

At usual doses, the primary concern is the effect the opioids have on respiratory function. Decreased tidal volume, depressed cough reflex and the drying of respiratory secretions may all have a detrimental effect on a susceptible patient. Bronchoconstriction (secondary to histamine release?) following IV doses has been noted in dogs.

Gastrointestinal effects may include: nausea, vomiting and decreased intestinal peristalsis. Dogs will usually defecate after an initial dose of morphine. Horses exhibiting signs of mild colic may have their symptoms masked by the administration of narcotic analgesics.

The CNS effects of morphine are dose and species specific. Animals that are stimulated by morphine, may elucidate changes in behavior, appear restless, and at very high doses, have convulsions. The CNS depressant effects seen in dogs may encumber the abilities of working animals.

Body temperature changes may be seen. Cattle, goats, horses and cats may exhibit signs of hyperthermia. while rabbits and dogs may develop hypothermia.

Chronic administration may lead to physical dependence.
**OVERDOSAGE**

Overdosage may produce profound respiratory and/or CNS depression in most species. Newborns may be more susceptible to these effects than adult animals. Parenteral doses greater than 100 mg/kg are thought to be fatal in dogs. Other toxic effects can include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia.

Some species such as horses, cats, swine, and cattle may demonstrate CNS excitability (hyperreflexia, tremors) and seizures at high doses or if given intravenously (rapidly). Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, animals should be closely observed as naloxone’s effects may diminish before sub-toxic levels of morphine are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

Pentobarbital has been suggested as a treatment for CNS excitement and seizures in cats. Extreme caution should be used as barbiturates and narcotics can have additive effects on respiratory depression.

**DRUG INTERACTIONS**

Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with morphine.

Morphine is contraindicated in patients receiving monamine oxidase (MAO) inhibitors (rarely used in veterinary medicine) for at least 14 days after receiving MAO inhibitors in humans. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of morphine while on these agents.

**LABORATORY INTERACTIONS**

Plasma amylase and lipase values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**DOSES**

**Dogs**

For analgesia (acute pain):
- a) 0.5 - 2 mg/kg IM or SC q3-4 hours. For SLOW IV administration use 10% of IM dose. (Hendrix and Hansen 2000)
- b) Using the oral sustained release product: 1.5 - 3 mg/kg PO q12h (Hardie 2000)

Epidural administration for pain control:
- a) 0.1 mg/kg. Dilution may be necessary for accurate measurement. Total volume administered not to exceed 0.3 ml/kg. (Mathews 1999)
- b) 0.1 mg/kg preservative free morphine; duration of action 12-24 hours (Thomas 2000)

As a preanesthetic:
- a) 0.1 - 2 mg/kg SC (Booth 1988a)

For adjunctive treatment of cardiogenic edema:
- a) 0.1 mg/kg IV q2-3 minutes prn to effect (reduction in dyspnea and anxiety), or 0.25 mg SC (Roudebush 1985)

For adjunctive treatment of supraventricular premature beats:
- a) 0.2 mg/kg IM or SC (Morgan 1988)

For treatment of hypermotile diarrhea:
- a) 0.25 mg/kg (Jones 1985a)

As an antitussive:
- a) 0.1 mg/kg q6-12h SC (Roudebush 1985)
Cats
For analgesia:
   a) 0.05 - 0.2 mg/kg SC, IM, may cause dysphoria if dose excessive (Carroll 1999)
   b) 0.1 - 0.4 mg/kg IM, SC q3-6h; concomitant tranquilization recommended (Hendrix and Hansen 2000)
Epidural administration for pain control:
   a) 0.1 mg/kg preservative free morphine; duration of action 12-24 hours (Thomas 2000)

Rabbits/Rodents/Pocket Pets
   a) Rabbits: 2 - 5 mg/kg IM or SC q2-4h for sedation and analgesia (Ivey and Morrisey 2000)

Horses
Note: ARCI UCGFS Class 1 Drug
For analgesia:
   a) 0.22 mg/kg IM or slow IV (Booth 1988a)
   b) 0.2 - 0.6 mg/kg IV (slowly); premedicate with xylazine (1 mg/kg IV) to reduce excitement (Jenkins 1987)
   c) 0.02 - 0.04 mg/kg IV (Muir 1987)
   d) 0.05 - 0.12 mg/kg IV (Thurmon and Benson 1987)
Note: Narcotics may cause CNS excitement in the horse. Some clinicians recommend pretreatment with acepromazine (0.02 - 0.04 mg/kg IV), or xylazine (0.3 - 0.5 mg/kg IV) to reduce the behavioral changes these drugs can cause.
Warning: Narcotic analgesics can mask the behavioral and cardiovascular symptoms associated with mild colic.

Swine
As a preanesthetic/analgesic (prior to chloralose/barbiturate):
   a) 0.2 - 0.9 mg/kg IM. Note: may cause undesirable stimulation. (Booth 1988a)
As an analgesic:
   a) 0.2 mg/kg up to 20 mg total dose IM (Jenkins 1987)

Sheep & Goats
As an analgesic:
   a) Up to 10 mg total dose IM (Jenkins 1987)

Monitoring Parameters
1) Respiratory rate/depth
2) CNS level of depression/excitation
3) Blood pressure if possible and indicated (especially with IV use)
4) Analgesic activity

Client Information
When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.
DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES

Veterinary-Approved Products
None

Human-Approved Products

Morphine Sulfate for Injection: 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 4 mg/ml, 5 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, 25 mg/ml, 50 mg/ml in amps and vials of sizes that range from 1 ml to 50 ml depending on manufacturer and concentration.

Morphine Sulfate for Injection (preservative-free): 0.5 mg/ml, 2 ml amps, 10 ml amps & vials; 1 mg/ml, 10 ml amps & vials; Infumorph® (ESI Lederle); Astramorph PF® (Astra)

Morphine Sulfate Soluble Tablets: 10 mg, 15 mg, 30 mg (Eli Lilly)

Morphine Sulfate Tablets: 15 mg, 30 mg (Roxane, Purdue Frederick)

Morphine Sulfate Extended/Controlled Release Tablets: 15 mg, 30 mg, 60 mg, 100 mg, 200 mg (Purdue Frederick, Roxane, Endo) CII

Morphine Sulfate Capsules: 15 mg, 30 mg (Purdue Frederick, Astra Zeneca)

Morphine Sulfate Sustained Release Capsules: 20 mg, 50 mg and 100 mg (Astra Zeneca)

Morphine Sulfate Oral Solution; 10 mg/5ml in 100 & 500 ml bts & unit dose (5, 10 ml) EDTA in 120 ml, Morphine Sulfate® (Roxane), MSIR® (Purdue Frederick); 10 mg/2.5 ml in UD 2.5 ml, Roxanol Rescudose® (Roxane), Roxanol UD® (Roxane); 20 mg/5ml in 100, 500 ml bts, EDTA in 120 ml & unit dose 5 ml, Morphine Sulfate® (Roxane), MSIR® (Purdue Frederick), Roxanol UD® (Roxane); 20 mg/ml in 30 & 120 ml, OMS Concentrate® (Upsher-Smith), Roxanol® (Roxane), Roxanol T® (Roxane); 30 mg 1.5 ml in UD 1.5 ml, Roxanol UD® (Roxane);100 mg/5 ml in 240 ml, Roxanol 100® (Roxane) CII

Morphine Sulfate Rectal Suppositories 5 mg, 10 mg & 20 mg, 30 mg in12's and 50's

Note: All morphine products are Rx and a Class-II controlled substance. Very accurate record keeping is required as to use and disposition of stock. See the appendix for more information.

NALOXONE HCl

PRESCRIBER HIGHLIGHTS
- Injectable opiate antagonist
- Contraindicated: hypersensitive to it. Caution: preexisting cardiac abnormalities or opioid dependent
- Reversal effect may be shorter than opioid effect, monitor and re-dose prn.

CHEMISTRY
An opiate antagonist, naloxone HCl is structurally related to oxymorphone. It occurs as a white to slightly off-white powder with a pK<sub>a</sub> of 7.94. Naloxone is soluble in water and slightly soluble in alcohol. The pH range of commercially available injectable solutions are from 3-4.5. Naloxone HCl may also be known as N-allylnoroxymorphine HCl.

STORAGE/STABILITY/COMPATIBILITY
Naloxone HCl for injection should be stored at room temperature (15-30°C) and protected from light.

Sterile water for injection is the recommended diluent for naloxone injection. When given as an IV infusion, either D<sub>2</sub>W or normal saline should be used. Naloxone HCl injection should not be mixed with solutions containing sulfites, bisulfites, long-chain or high molecular weight anions or any solutions at alkaline pH.
PHARMACOLOGY
Naloxone is considered to be a pure opiate antagonist and it has basically no analgesic activity. The exact mechanism for its activity is not understood, but it is believed that the drug acts as a competitive antagonist by binding to the \textit{mu}, \textit{kappa}, and \textit{sigma} opioid receptor sites. The drug apparently has its highest affinity for the \textit{mu} receptor.

Naloxone reverses the majority of effects associated with high-dose opiate administration (respiratory and CNS depression). In dogs, naloxone apparently does not reverse the emetic actions of apomorphine.

Naloxone also has other pharmacologic activity at high doses, including effects on dopaminergic mechanisms (increases dopamine levels) and GABA antagonism.

USES/INDICATIONS
Naloxone is used in veterinary medicine almost exclusively for its opiate reversal effects, but the drug is being investigated for treating other conditions (e.g., septic, hypovolemic or cardiogenic shock). Naloxone may also be employed as a test drug to see if endogenous opiate blockade will result in diminished tail-chasing or other self-mutilating behaviors.

PHARMACOKINETICS
Naloxone is only minimally absorbed when given orally as it is rapidly destroyed in the GI tract. Much higher doses are required if using this route of administration for any pharmacologic effect. When given IV, naloxone has a very rapid onset of action (usually 1–2 minutes). If given IM, the drug generally has an onset of action within 5 minutes of administration. The duration of action usually persists from 45–90 minutes, but may act for up to 3 hours.

Naloxone is distributed rapidly throughout the body with high levels found in the brain, kidneys, spleen, skeletal muscle, lung and heart. The drug also readily crosses the placenta.

Naloxone is metabolized in the liver, principally via glucuronidative conjugation with metabolites excreted into the urine. In humans, the serum half-life is approximately 60–100 minutes.

CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY
Naloxone is contraindicated in patients hypersensitive to it. It should be used cautiously in animals that have preexisting cardiac abnormalities or in animals that may be opioid dependent. The veterinary manufacturer states to use the drug "...cautiously in animals who have received exceedingly large doses of narcotics. ... may produce an acute withdrawal syndrome and smaller doses should be employed." (Package Insert; \textit{P/M® Naloxone HCl Injection-P/M}; Mallinckrodt)

Naloxone is generally considered to be non-teratogenic in animals, but has precipitated withdrawal in opioid-dependent human fetuses.

ADVERSE EFFECTS/Warnings
At usual doses, naloxone is relatively free of adverse effects in non-opioid dependent patients.

Because the duration of action of naloxone may be shorter than that of the narcotic being reversed, animals that are being treated for opioid intoxication or with symptoms of respiratory depression should be closely monitored as additional doses of naloxone and/or ventilatory support may be required.

OVERDOSE/Acute TOXICITY
Naloxone is considered to be a very safe agent with a very wide margin of safety, but very high doses have initiated seizures (secondary to GABA antagonism?) in a few patients.

DRUG INTERACTIONS
Naloxone also reverses the effects of opioid agonists/antagonists such as butorphanol, pentazocine or nalbuphine.
DOSES

Dogs & Cats
For opioid reversal:
   a) 0.002 - 0.02 mg/kg IV or IM; duration of effect 0.5-1 hour. (Bednarski 1989)
   b) Dogs: 0.04 mg/kg IV, IM or SC (Package Insert; P/M® Naloxone HCl Injection -P/M; Mallinckrodt), (Kirk 1989)
   c) Cats: 0.05 - 0.1 mg/kg IV (Muir and Swanson 1989)
   d) 0.02 - 0.04 mg/kg IV (Morgan 1988)

Rabbits/Rodents/Pocket Pets:
   a) For opioid reversal in rodents: 0.01 - 0.1 mg/kg SC or IP as needed (Huerkamp 1995)
   b) Rabbits: 0.005 - 0.1 mg/kg IM or IV (Ivey and Morrisey 2000)
   c) Hamsters, Gerbils, Mice, Rats, Guinea pigs, Chinchillas: 0.01 - 0.1 mg/kg SC, IP (Adamcak and Otten 2000)

Horses
For opioid reversal:
   a) 0.01 - 0.022 mg/kg to reverse sedative and excitatory effects of narcotic agonists. (Clark and Becht 1987)
   b) 0.01 mg/kg IV to limit increases in locomotor activity secondary to narcotic agonists. (Muir 1987)
   c) 0.01 - 0.02 mg/kg IV (Robinson 1987)

MONITORING PARAMETERS
1) Respiratory rate/depth; 2) CNS function; 3) Pain associated with opiate reversal

CLIENT INFORMATION
Should be used with direct professional supervision only.

DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES

Veterinary-Approved Products
None

Human-Approved Products
   Naloxone HCl Injection 0.4 mg/ml in 1 ml amps, syringes & 1, 2, & 10 ml vials; Narcan® (DuPont Pharm.), Generic; (Rx)
   Naloxone HCl Injection 1 mg/ml in 2 ml amps, & 10 ml vials; Narcan® (DuPont Pharm.); (Rx)
   Naloxone HCl Neonatal Injection 0.02 mg/ml in 2 ml amps, & vials; Narcan® (DuPont Pharm); Generic; (Rx)
NEOSTIGMINE BROMIDE
NEOSTIGMINE Methylsulfate

PRESCRIBER HIGHLIGHTS

- Parasympathomimetic used to initiate peristalsis, empty the bladder and stimulating skeletal muscle contractions. Also for dx and tx of myasthenia gravis and tx of non-depolarizing neuromuscular blocking agents (curare-type) OD's.
- Contraindicated: peritonitis, mechanical intestinal or urinary tract obstructions, late stages of pregnancy, hypersensitive to this class of compounds or treated with other cholinesterase inhibitors
- Adverse effects: cholinergic in nature and dose related (nausea, vomiting, diarrhea, excessive salivation and drooling, sweating, miosis, lacrimation, increased bronchial secretions, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, muscle cramps and weakness, agitation, restlessness or paralysis).
- Don't confuse cholinergic crisis and myasthenic crisis
- Drug Interactions

CHEMISTRY
Synthetic quaternary ammonium parasympathomimetic agents, neostigmine bromide and neostigmine methylsulfate both occur as odorless, bitter-tasting, white, crystalline powders that are very soluble in water and soluble in alcohol. The melting point of neostigmine methylsulfate is from 144-149°. The pH of the commercially available neostigmine methylsulfate injection is from 5-6.5.

STORAGE/Stability/Compatibility
Neostigmine bromide tablets should be stored at room temperature in tight containers. Neostigmine methylsulfate injection should be stored at room temperature and protected from light; avoid freezing.

Neostigmine methylsulfate injection is reportedly physically compatible with the commonly used IV replacement solutions and the following drugs: glycopyrrolate, pentobarbital sodium, and thiopental sodium.

PHARMACOLOGY
Neostigmine competes with acetylcholine for acetylcholinesterase. As the neostigmine-acetylcholinesterase complex is hydrolyzed at a slower rate than that of the acetylcholine-enzyme complex, acetylcholine will accumulate with a resultant exaggeration and prolongation of its effects. These effects can include increased tone of intestinal and skeletal musculature, stimulation of salivary and sweat glands, bronchoconstriction, ureter constriction, miosis and bradycardia. Neostigmine also has a direct cholinomimetic effect on skeletal muscle.

USES/INDICATIONS
Neostigmine is indicated for rumen atony, initiating peristalsis, emptying the bladder and stimulating skeletal muscle contractions in cattle, horses, sheep and swine (Package insert; Stiglyn® 1:500 - P/M; Mallinckrodt). It has also been used in the diagnosis and treatment of myasthenia gravis and in treating non-depolarizing neuromuscular blocking agents (curare-type) overdoses in dogs.

PHARMACOKINETICS
Information on the pharmacokinetics of neostigmine in veterinary species was not located. In humans, neostigmine bromide is poorly absorbed after oral administration with only 1-2% of the dose absorbed. Neostigmine effects on peristaltic activity in humans begin within 10-30 minutes after parenteral administration and can persist for up to 4 hours.

Neostigmine is 15-25% bound to plasma proteins. It has not been detected in human milk nor would be expected to cross the placenta when given at usual doses.

In humans, the half-life of the drug is approximately one hour. It is metabolized in the liver and also hydrolyzed by cholinesterases to 3-OH PTM which is weakly active. When administered parenterally, approximately 80% of the drug is excreted in the urine within 24 hours, with 50% excreted unchanged.
CONTRAINDICATIONS/PRECAUTIONS
Neostigmine is contraindicated in patients with peritonitis, mechanical intestinal or urinary tract obstructions, late stages of pregnancy, in animals hypersensitive to this class of compounds or treated with other cholinesterase inhibitors.

Use neostigmine with caution in patients with epilepsy, peptic ulcer disease, bronchial asthma, cardiac arrhythmias, hyperthyroidism, vagotonia or megacolon.

ADVERSE EFFECTS/WARNINGS
Adverse effects of neostigmine are dose-related and cholinergic in nature. See overdosage section below.

OVERDOSAGE
Overdosage of neostigmine can induce a cholinergic crisis. Symptoms can include nausea, vomiting, diarrhea, excessive salivation and drooling, sweating (in animals with sweat glands), miosis, lacrimation, increased bronchial secretions, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, muscle cramps and weakness, agitation, restlessness or paralysis. In patients with myasthenia gravis, it may be difficult to distinguish between a cholinergic crisis and myasthenic crisis. A test dose of edrophonium, should differentiate between the two.

Cholinergic crisis is treated by temporarily ceasing neostigmine therapy and instituting treatment with atropine (doses are listed in the Atropine monograph). Maintain adequate respirations using mechanical assistance if necessary.

DRUG INTERACTIONS
Anticholinesterase therapy may be antagonized by administration of parenteral magnesium therapy, as it can have a direct depressant effect on skeletal muscle.

Drugs that possess some neuromuscular blocking activity (e.g., aminoglycoside antibiotics, some antiarrhythmic and anesthetic drugs) may necessitate increased dosages of neostigmine in treating or diagnosing myasthenic patients.

Corticosteroids may decrease the anticholinesterase activity of neostigmine. After stopping corticosteroid therapy, neostigmine may cause increased anticholinesterase activity.

Neostigmine may prolong the Phase I block of depolarizing muscle relaxants (e.g., succinylcholine, decamethonium). Neostigmine antagonizes the actions of non-depolarizing neuromuscular blocking agents (pancuronium, tubocurarine, gallamine, etc.).

Atropine will antagonize the muscarinic effects of neostigmine and is often used to reduce neostigmine’s side effects. Use cautiously however, as atropine can mask the early symptoms of cholinergic crisis.

Theoretically, dexpanthenol may have additive effects when used with neostigmine.

DOSES
Dogs
- For treatment of myasthenia gravis:
  - a) 0.04 mg/kg IM q6h to bypass the problem of oral medication in actively regurgitating animals. (Inzana 2000)

- For diagnosis of myasthenia gravis:
  - a) 0.05 mg/kg IM (Diagnostic if clinical improvement occurs in 15-30 minutes; pre-treat with atropine) (LeCouteur 1988)

- For treatment of curare overdoses:
  - a) 0.001 mg/kg SC, follow with IV injection of atropine (0.04 mg/kg) (Bailey 1986)

Cats
- For treatment of myasthenia gravis:
  - a) 0.04 mg/kg IM q6h to bypass the problem of oral medication in actively regurgitating animals. (Inzana 2000)
Cattle

a) 1 mg/100 lbs of body weight SC; repeat as indicated (Package Insert; Stiglyn® 1:500 - P/M; Mallinckrodt)

Horses

Note: ARCI UCGFS Class 3 Drug

a) 1 mg/100 lbs of body weight SC; repeat as indicated (Package Insert; Stiglyn® 1:500 - P/M; Mallinckrodt)

For treatment of paralytic ileus of large colon:

a) 2 - 4 mg SC q2h. Use after correction of large bowel displacement; discontinue when GI motility returns. May cause increased secretion into GI tract and therefore may be harmful in small intestinal disease. Does not produce progressive contractions of small intestine. (Stover 1987)

b) 0.02 mg/kg SC; duration of action may be very short (15-30 minutes); does not increase propulsive motility of jejunum and may delay gastric emptying time. (Clark and Becht 1987)

c) 0.44 mg/kg (approximately 2 mg total dose for a 450 kg horse) SC or IV; may be repeated every 1/2 to 2 hours. If ineffective and no adverse effects seen, may increase dose in 2 mg increments to a total of 10 mg per treatment. (Moore 1999)

Swine

a) 2 - 3 mg/100 lbs of body weight IM; repeat as indicated (Package Insert; Stiglyn® 1:500 - P/M; Mallinckrodt)

b) 0.03 mg/kg (Davis 1986)

Sheep

a) 1.0 - 1.5 mg/100 lbs of body weight SC; repeat as indicated (Package Insert; Stiglyn® 1:500 - P/M; Mallinckrodt)

b) 0.01 - 0.02 mg/kg (goats also) (Davis 1986)

**MONITORING PARAMETERS**

Dependent on reason for use.

1) Adverse reactions (see Adverse Reactions and Overdosage above)

2) Clinical efficacy

**CLIENT INFORMATION**

This product should be used by professionals in situations where the drug’s effects can be monitored.

**DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHOLDING TIMES**

**Veterinary-Approved Products**

None

**Human-Approved Products**

Neostigmine Methylsulfate Injection 1:1000 (1 mg/ml), 1:2000 (0.5 mg/ml), 1:4000 (0.25 mg/ml) in 1 ml amps and 10 ml vials; Prostigmin® (ICN); Generic; (Rx)
OXYMORPHONE HCl

PRESCRIBER HIGHLIGHTS
- Injectable opiate sedative/restraining agent, analgesic and preanesthetic
- Contraindications: hypersensitive to it, diarrhea caused by a toxic ingestion. Caution: hypothyroidism, severe renal insufficiency (acute uremia), adrenocortical insufficiency, geriatric or severely debilitated patients, head injuries or increased intracranial pressure and acute abdominal conditions (e.g., colic). Extreme caution: respiratory disease or from acute respiratory dysfunction.
- Adverse Effects: respiratory depression and bradycardia. Decreased GI motility with resultant constipation possible. Cats (high dosages): ataxia, hyperesthesia and behavioral changes (without concomitant tranquilization).
- Availability and expense are issues
- Drug-drug; drug-lab interactions
- C-II controlled substance

CHEMISTRY
A semi-synthetic phenanthrene narcotic agonist, oxymorphone HCl occurs as odorless white crystals or white to off-white powder. It will darken in color with prolonged exposure to light. One gram of oxymorphone HCl is soluble in 4 ml of water and it is sparingly soluble in alcohol and ether. The commercially available injection has a pH of 2.7 - 4.5.

STORAGE/STABILITY/COMPATIBILITY
The injection should be stored protected from light and at room temperature (15-30° C); avoid freezing. The commercially available suppositories should be stored at temperatures between 2° and 15° C. Oxymorphone has been reported to be physically compatible when mixed with acepromazine, atropine, and glycopyrrolate. It is physically incompatible when mixed with barbiturates, and diazepam.

PHARMACOLOGY
Receptors for opiate analgesics are found in high concentrations in the limbic system, spinal cord, thalamus, hypothalamus, striatum, and midbrain. They are also found in tissues such as the gastrointestinal tract, urinary tract, and in other smooth muscle.

Opiate receptors are further broken down into five main sub-groups. Mu receptors are found primarily in the pain regulating areas of the brain. They are thought to contribute to the analgesia, euphoria, respiratory depression, physical dependence, miosis, and hypothermic actions of opiates. Kappa receptors are located primarily in the deep layers of the cerebral cortex and spinal cord. They are responsible for analgesia, sedation and miosis. Sigma receptors are thought to be responsible for the dysphoric effects (struggling, whining), hallucinations, respiratory and cardiac stimulation, and mydriatic effects of opiates. Delta receptors, located in the limbic areas of the CNS and epsilon receptors have also been described, but their actions have not been well explained at this time.

The morphine-like agonists (morphine, meperidine, oxymorphone) have primary activity at the mu receptors, with some activity possible at the delta receptor. The primary pharmacologic effects of these agents include: analgesia, antitusive activity, respiratory depression, sedation, emesis, physical dependence, and intestinal effects (constipation/defecation). Secondary pharmacologic effects include: CNS: euphoria, sedation, & confusion. Cardiovascular: bradycardia due to central vagal stimulation, alpha-adrenergic receptors may be depressed resulting in peripheral vasodilation, decreased peripheral resistance, and baroreceptor inhibition. Orthostatic hypotension and syncope may occur. Urinary: Increased bladder sphincter tone can induce urinary retention.

Various species may exhibit contradictory effects from these agents. For example, horses, cattle, swine, and cats may develop excitement after morphine injections and dogs may defecate after morphine. These effects are in contrast to the expected effects of sedation and constipation. Dogs and humans may develop miosis, while other species (especially cats) may develop mydriasis. For more information see the individual monographs for each agent.

Oxymorphone is approximately 10 times more potent an analgesic on a weight basis when compared to morphine. It has less antitusive activity than does morphine. In humans, it has more of a tendency to cause increased nausea and vomiting than does morphine, while in dogs the opposite appears to be true. At the usual doses employed, oxymorphone alone has good sedative qualities in the dog.
Respiratory depression can occur especially in debilitated, neonatal or geriatric patients. Bradycardia, as well as a slight decrease in cardiac contractility and blood pressure may also be seen. Like morphine, oxymorphone does initially increase the respiratory rate (panting in dogs) while actual oxygenation may be decreased and blood CO₂ levels may increase by 10 mmHg or more. Gut motility is decreased with resultant increases in stomach emptying times. Unlike either morphine or meperidine, oxymorphone does not appear to cause histamine release.

**Pharmacokinetics**

Oxymorphone is absorbed when given by IV, IM, SC, and rectal routes. Although absorbed when given orally bioavailability is reduced, probably from a high first-pass effect. After IV administration, analgesic efficacy usually occurs within 3-5 minutes.

Like morphine, oxymorphone concentrates in the kidney, liver, and lungs; lower levels are found in the CNS. Oxymorphone crosses the placenta and narcotized newborns can result if mothers are given the drug before giving birth, but these effects can be rapidly reversed with naloxone.

The drug is metabolized in the liver; primarily by glucuronidation. Because cats are deficient in this metabolic pathway, half-lives in cats are probably prolonged. The glucuronidated metabolite is excreted by the kidney.

**Uses/Indications**

Oxymorphone is used in dogs and cats as a sedative/restraining agent, analgesic and preanesthetic and occasionally in horses as an analgesic and anesthesia induction agent. It may also be used in swine as an adjunctive analgesic with ketamine/xylazine anesthesia and in small rodents as an analgesic/anesthetic for minor surgical procedures.

**Contraindications/Precautions**

All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison’s), and in geriatric or severely debilitated patients. Oxymorphone is contraindicated in patients hypersensitive to narcotic analgesics, and in patients taking monamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Oxymorphone should be used with extreme caution in patients with head injuries, increased intracranial pressure and acute abdominal conditions (e.g., colic) as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (e.g., pulmonary edema secondary to smoke inhalation).

Oxymorphone can cause bradycardia and therefore should be used cautiously in patients with preexisting bradyarrhythmias.

Neonatal, debilitated or geriatric patients may be more susceptible to the effects of oxymorphone and may require lower dosages. Patients with severe hepatic disease may have prolonged duration's of action of the drug. If used in cats at high dosages, the drug has been recommended to be given along with a tranquilizing agent, as oxymorphone can produce bizarre behavioral changes in this species. This also is true in cats also for the other opiate agents, such as morphine.

Opiate analgesics are also contraindicated in patients who have been stung by the scorpion species *Centruroides sculpturatus* Ewing and *C. gertschi* Stahnke as it may potentiate these venoms.

**Adverse Effects/Warnings**

Oxymorphone may cause respiratory depression and bradycardia (see above). When used in cats at high dosages, oxymorphone may cause ataxia, hyperesthesia and behavioral changes (without concomitant tranquilization). Decreased GI motility with resultant constipation has also been described.
OVERDOSAGE
Massive overdoses may produce profound respiratory and/or CNS depression in most species. Other effects may include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, and animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of oxymorphone are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

DRUG INTERACTIONS
Other CNS depressants (e.g., anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with oxymorphone. Oxymorphone is contraindicated in patients receiving monoamine oxidase (MAO) inhibitors (rarely used in veterinary medicine) for at least 14 days after receiving MAO inhibitors in humans. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of oxymorphone while on these agents.

LABORATORY INTERACTIONS
Plasma amylase and lipase values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

DOSES

Dogs
For sedation for minor procedures:
   a) up to 0.2 mg/kg IM or IV; initially a maximum of 5 mg total dose (Combine with acepromazine 0.05 - 0.1 mg/kg IM or IV) (Shaw et al. 1986)
   b) 0.05 - 0.1 mg/kg IV or 0.1 - 0.2 mg/kg IM, SC (Morgan 1988)

For analgesia (acute pain):
   a) 0.1 - 0.2 mg/kg IM, IV, or SC q1-3h (Hendrix and Hansen 2000)
   b) Epidural administration: 0.05 mg/kg. Dilution may be necessary for accurate measurement. Total volume administered not too exceed 0.3 ml/kg. (Mathews 1999)
   c) 0.05 - 0.1 mg/kg IV, IM, SC; maximum dose of 4 mg. May cause more respiratory depression than butorphanol. (Mathews 1999)

For premedication to anesthesia in healthy dogs:
   a) 0.1 - 0.2 mg/kg IM or IV (used with acepromazine and atropine or glycopyrrolate unless contraindicated. Thiopental/thiamylal dose may be reduced to 2 - 4 mg/kg when using high end of oxymorphone dose). (Shaw et al. 1986)

Induction of anesthesia in geriatric or sick dogs:
   a) 0.1 - 0.2 mg/kg IM or IV; give incrementally to effect (administered alternately with diazepam at 0.2 - 0.5 mg/kg; use with atropine or glycopyrrolate unless contraindicated; follow with halothane, methoxyflurane or isoflurane) (Shaw et al. 1986)

Facilitation of inhalation anesthesia without thiobarbiturates or ketamine in sight hounds:
   a) up to 0.2 mg/kg IV or IM (Combine with acepromazine; use with atropine or glycopyrrolate unless contraindicated) (Shaw et al. 1986)

Cats
For restraint/sedation for minor procedures:
   a) 0.05 mg/kg IV, SC or IM; may cause dysphoria in cats without pain or with excessive dose (Carroll 1999)
   b) 0.025 - 0.1 mg/kg IV (must be given with tranquilizer; e.g., acepromazine 0.1 mg/kg) (Shaw et al. 1986)
   c) 0.02 - 0.03 mg/kg IV or IM with or without another tranquilizer (Mandsager 1988)
As a preanesthetic/analgesic:
  a) 0.1 - 0.4 mg/kg IV (Shaw et al. 1986)

As an analgesic (acute pain):
  a) 0.05 - 0.1 mg/kg IM, SC or IV q1-3h; concomitant tranquilization recommended (Hendrix and Hansen 2000)

Ferrets
  a) 0.05 - 0.2 mg/kg IV or IM 2-4 times daily (Williams 2000)

Rabbits/Rodents/Pocket Pets
  a) **Rabbits**: 0.2 mg/kg IM q2-4h (Ivey and Morrisey 2000)
  b) Anesthetic/analgesic for minor surgical procedures: 0.15 mg/kg IM (for a hamster-sized animal) (Shaw et al. 1986)
  c) **Hamsters, Gerbils, Mice, Rats, Guinea pigs**: 0.2 - 0.5 mg/kg SC, IM q6-12h for analgesia (Adamcak and Otten 2000)

Horses
  Note: ARCI UCGFS Class 1 Drug

As an analgesic:
  a) 0.01 - 0.02 mg/kg IV (Muir 1987)
  b) 0.01 - 0.022 mg/kg IV; up to 15 mg total (divide dose into 3-4 increments and give several minutes apart (Shaw et al. 1986)
  c) 0.02 - 0.03 mg/kg IM (Robinson 1987)
  d) 0.015 - 0.03 mg/kg IV (Thurmon and Benson 1987)

Anesthetic induction in severely compromised horses:
  a) 0.01 - 0.022 mg/kg IV (after approx. 45 minutes, may be necessary to "top off" with another 1/3 of the original dose) (Shaw et al. 1986)
  
  **Note:** Narcotics (oxymorphone included) may cause CNS excitement in the horse. Some clinicians recommend pretreatment with acepromazine (0.02 - 0.04 mg/kg IV), or xylazine (0.3 - 0.5 mg/kg IV) to reduce the behavioral changes these drugs can cause.

  **Warning:** Narcotic analgesics can mask the behavioral and cardiovascular symptoms associated with mild colic.

Swine
  To increase analgesia when used with ketamine (2 mg/kg)/xylazine (2 mg/kg):
    a) 0.075 mg/kg IV (duration of anesthesia and recumbency: 20 - 30 minutes) (Shaw et al. 1986)

**MONITORING PARAMETERS**
  1) Respiratory rate/depth
  2) CNS level of depression/excitation
  3) Blood pressure if possible and indicated (especially with IV use)
  4) Analgesic activity
  5) Cardiac rate

**CLIENT INFORMATION**
When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.

**DOSE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**
  None
Human-Approved Products

Oxymorphone HCl for Injection 1 mg/ml in 1 ml amps; 1.5 mg/ml in 10 ml vials; Numorphan® (Endo Labs); (Rx)

Oxymorphone HCl 5 mg suppositories in 6s.; Numorphan® (Endo Labs); (Rx)

Note: Oxymorphone is a Class-II controlled substance. Very accurate record keeping is required as to use and disposition of stock.

**PHENOBARBITAL SODIUM**

**PHENOBARBITAL**

**PRESCRIBER HIGHLIGHTS**

- Barbiturate used primarily as an antiseizure medication; also used as a sedative agent
- Contraindicated: Known hypersensitivity, severe liver disease, nephritis or severe respiratory depression (large doses). Caution: hypovolemia, anemia, borderline hypoadrenal function, or cardiac or respiratory disease. Use w/caution in cats (sensitive to respiratory depression)
- Adverse Effects: Dogs: anxiety/agitation or lethargy (when initiating tx). Profound depression (even at low doses) possible. Sedation, ataxia, polydipsia, polyuria, polyphagia can be seen at moderate to high serum levels. Increase in liver enzymes possible, but overt hepatotoxicity relatively uncommon. Rare: anemia, thrombocytopenia or neutropenia. Cats: ataxia, lethargy, polyphagia/weight gain and polydipsia/polyuria. Rare: immune-mediated reactions and bone marrow hypoplasia.
- When administering IV, give SLOWLY; do not give SC or perivascularly (very irritating)
- Drug Interactions; drug-lab interactions
- C-IV controlled substance

**CHEMISTRY**

Phenobarbital, a barbiturate, occurs as white, glistening, odorless, small crystals or as a white, crystalline powder with a melting point of 174°-178°C and a pKₐ of 7.41. One gram is soluble in approximately 1000 ml of water, and 10 ml of alcohol. Compared to other barbiturates it has a low lipid solubility.

Phenobarbital sodium occurs as bitter-tasting, white, odorless, flaky crystals or crystalline granules or powder. It is very soluble in water, soluble in alcohol, and freely soluble in propylene glycol. The injectable product has a pH of 8.5-10.5.

**STORAGE/Stability/Compatibility**

Aqueous solutions of phenobarbital are not very stable. Propylene glycol is often used in injectable products to help stabilize the solution. Solutions of phenobarbital sodium should not be added to acidic solutions nor used if they contain a precipitate or are grossly discolored.

The following solutions and drugs have been reported to be **physically compatible** with phenobarbital sodium: Dextrose IV solutions, Ringer’s injection, lactated Ringer’s injection, Saline IV solutions, dextrose-saline combinations, dextrose-Ringer’s combinations, dextrose-Ringer’s lactate combinations, amikacin sulfate, aminophylline, atrazine sulfate (for at least 15 minutes, not 24 hours), calcium chloride and gluconate, cephalirin sodium, dimenhydrinate, polymyxin B sulfate, sodium bicarbonate, thiopental sodium, and verapamil HCl.

The following drugs have been reported to be **physically incompatible** with phenobarbital sodium: benzquinamide HCl, cephalothin sodium, chlorpromazine HCl, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrrolate, hydralazine HCl, hydrocortisone sodium succinate, hydroxyzine HCl, insulin (regular), meperidone HCl, morphine sulfate, naltrexone HCl, norepinephrine bitartrate, oxytetracycline HCl, pentazocine lactate, procaine HCl, procchronperazine edisylate, promazine HCl, promethazine HCl, and streptomycin sulfate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references (e.g., Trissel - see bibliography) for more specific information.
PHARMACOLOGY

While barbiturates are generally considered to be CNS depressants, they can invoke all levels of CNS mood alteration from paradoxical excitement to deep coma and death. While the exact mechanisms for the CNS effects caused by barbiturates are unknown, they have been shown to inhibit the release of acetylcholine, norepinephrine, and glutamate. The barbiturates also have effects on GABA and pentobarbital has been shown to be GABA-mimetic. At high anesthetic doses, barbiturates have been demonstrated to inhibit the uptake of calcium at nerve endings.

The degree of depression produced is dependent on the dosage, route of administration, pharmacokinetics of the drug, and species treated. Additionally, effects may be altered by the age or physical condition of the patient, or the concurrent use of other drugs. The barbiturates depress the sensory cortex, lessen motor activity, and produce sedation at low dosages. Some barbiturates such as phenobarbital are useful as anticonvulsants because they tend to have sufficient motor activity depression, without causing excessive sedation. In humans, it has been shown that barbiturates reduce the rapid-eye movement (REM) stage of sleep. Barbiturates have no true intrinsic analgesic activity.

In most species, barbiturates cause a dose-dependent respiratory depression, but in some species they can cause slight respiratory stimulation. At sedative/hypnotic doses respiratory depression is similar to that during normal physiologic sleep. As doses increase, the medullary respiratory center is progressively depressed with resultant decreases in rate, depth, and volume. Respiratory arrest may occur at 4 times lower the dose that will cause cardiac arrest. These drugs must be used very cautiously in cats as they are particularly sensitive to the respiratory depressant effects of barbiturates.

Besides the cardiac arresting effects of the barbiturates at euthanatizing dosages, the barbiturates have other cardiovascular effects. In the dog, pentobarbital has been demonstrated to cause tachycardia, decreased myocardial contractility and stroke volume, and decreased mean arterial pressure and total peripheral resistance.

The barbiturates cause reduced tone and motility of the intestinal musculature, probably secondary to its central depressant action. The thiobarbiturates (thiamylal, thiopental) may, after initial depression, cause an increase in both tone and motility of the intestinal musculature. However, these effects do not appear to have much clinical significance. Administration of barbiturates reduces the sensitivity of the motor end-plate to acetylcholine, thereby slightly relaxing skeletal muscle. Because the musculature is not completely relaxed, other skeletal muscle relaxants may be necessary for surgical procedures.

There is no direct effect on the kidney by the barbiturates, but severe renal impairment may occur secondary to hypotensive effects in overdose situations. Liver function is not directly affected when used acutely, but hepatic microsomal enzyme induction is well documented with extended barbiturate (especially phenobarbital) administration. Although barbiturates reduce oxygen consumption of all tissues, no change in metabolic rate is measurable when given at sedative dosages. Basal metabolic rates may be reduced with resultant decreases in body temperature when barbiturates are given at anesthetic doses.

USES/INDICATIONS

Because of its favorable pharmacokinetic profile, relative safety and efficacy, low cost, and ability to treat epilepsy at sub-hypnotic doses, phenobarbital is generally considered to be the drug of first choice when treating idiopathic epilepsy in dogs and cats. It is also occasionally used as an oral sedative agent in these species. Because it has a slightly longer onset of action, it is used principally in the treatment of status epilepticus in dogs, cats and horses to prevent the recurrence of seizures after they have been halted with either a benzodiazepine or short-acting barbiturate. Phenobarbital is also useful in controlling excessive feline vocalization while riding in automobiles.

In cattle, the microsomal enzyme stimulating properties of phenobarbital have been suggested for its use in speeding the detoxification of organochlorine (chlorinated hydrocarbon) insecticide poisoning. Additionally, phenobarbital has been used in the treatment and prevention of neonatal hyperbilirubinemia in human infants. It is unknown if hyperbilirubinemia is effectively treated in veterinary patients with phenobarbital.

PHARMACOKINETICS

The pharmacokinetics of phenobarbital have been thoroughly studied in humans and studied in a more limited fashion in dogs, cats and horses. Phenobarbital is slowly absorbed from the GI tract. Bioavailabilities range from 70-90% in humans, approximately 90% in dogs and absorption is practically complete in adult horses. Peak levels occur in 4-8 hours after oral dosing in dogs, and in 8-12 hours in humans.
Phenobarbital is widely distributed throughout the body, but because of its lower lipid solubility it does not distribute as rapidly as most other barbiturates into the CNS. The amount of phenobarbital bound to plasma proteins has been reported to be 40-50%. The reported apparent volumes of distribution are approximately: Horse ~ 0.8 L/kg; Foals ~ 0.86 L/kg; Dogs ~ 0.75 L/kg.

The drug is metabolized in the liver primarily by hydroxylated oxidation to p-hydroxyphenobarbital. Sulfate and glucuronide conjugates are also formed. The elimination half-lives reported in humans range from 2-6 days; in dogs from 12-125 hours with an average of approximately 2 days. Because of its ability to induce the hepatic enzymes used to metabolize itself (and other drugs), elimination half lives may decrease with time with concomitant reductions in serum levels. Some dogs may have half lives of less than 24 hours and may require 3 times daily dosing for maximal control. Elimination half lives of 34-43 hours have been reported in cats. Elimination half lives in horses are considerably shorter with values reported of approximately 13 hours in foals and 18 hours in adult horses. Phenobarbital will induce hepatic microsomal enzymes and it can be expected that elimination half-lives will decrease with time. Approximately 25% of a dose is excreted unchanged by the kidney. By alkalinizing the urine and/or substantially increasing urine flow, excretion rates can be increased. Anuric or oliguric patients may accumulate unmetabolized drug and dosage adjustments may need to be made in these patients.

Changes in diet, body weight, and body composition may alter the pharmacokinetics of phenobarbital in dogs and necessitate dosage adjustment.

**CONTRAINDICATIONS/Precautions**

Use cautiously in patients who are hypovolemic, anemic, have borderline hypoadrenal function, or cardiac or respiratory disease. Large doses are contraindicated in patients with nephritis or severe respiratory dysfunction. Barbiturates are contraindicated in patients with severe liver disease or who have demonstrated previous hypersensitivity reactions to them.

When administering IV, give slowly (not more than 60 mg/minute). Too rapid IV administration may cause respiratory depression. Commercially available injectable preparations (excluding the sterile powder) must not be administered subcutaneously or perivascularly as significant tissue irritation and possible necrosis may result. Applications of moist heat and local infiltration of 0.5% procaine HCl solution have been recommended to treat these reactions.

**Adverse Effects/Warnings**

Dogs may exhibit increased symptoms of anxiety/agitation or lethargy when initiating therapy. These effects are generally transitory in nature. Occasionally dogs will exhibit profound depression at lower dosage ranges (and plasma levels). Polydipsia, polyuria, and polyphagia are also quite commonly displayed at moderate to high serum levels and may falsely infer a diagnosis of Cushing's Disease; however these signs are usually controlled by limiting intake of both food and water. Sedation and/or ataxia often become significant concerns as serum levels reach the higher ends of the therapeutic range. Rarely, anemia, thrombocytopenia or neutropenia may occur which is reversible if detected early. Increases in liver enzymes are well described for phenobarbital in dogs and are not necessarily indicative of liver dysfunction. Frank hepatic failure is uncommon and is usually associated with higher serum levels (>30-40 mcg/ml).

Cats may develop ataxia, lethargy, polyphagia/weight gain and polydipsia/polyuria. Rarely immune-mediated reactions and bone marrow hypoplasia may be seen. Cats, unlike dogs, apparently do not have the issues of increased liver enzymes.

Although there is much less information regarding its use in horses (and in particular foals), it would be generally expected that adverse effects would mirror those seen in other species.

**Overdose**

Treatment of phenobarbital overdose consists of removal of ingested product from the gut if appropriate and offering respiratory and cardiovascular support. Activated charcoal has been demonstrated to be of considerable benefit in enhancing the clearance of phenobarbital, even when the drug was administered parenterally. Charcoal acts as a "sink" for the drug to diffuse from the vasculature back into the gut. Forced alkaline diuresis can also be of substantial benefit in augmenting the elimination of phenobarbital in patients with normal renal function. Peritoneal dialysis or hemodialysis may be helpful in severe intoxications or in anuric patients.
**Drug Interactions**

The following drugs may increase the effect of phenobarbital: **Other CNS depressants** (narcotics, phenothiazines, antihistamines, etc), valproic acid, and chloramphenicol.

Phenobarbital may decrease the effect of the following drugs: oral anticoagulants, chloramphenicol, corticosteroids, doxycycline, beta-blockers (propranolol), quinidine, theophylline, metronidazole. Pentobarbital with furosemide may cause or increase postural hypotension. Barbiturates may affect the metabolism of phenytoin; monitoring of blood levels may be indicated.

**Rifampin** may induce hepatic microsomal enzymes and reduce the half-life and effect of phenobarbital.

Phenobarbital may decrease the absorption of griseofulvin if given concurrently.

**Drug/Lab Interactions**

Barbiturates may cause increased retention of bromosulfophthalein (BSP; sulfobromophthalein) and give falsely elevated results. It is recommended that barbiturates not be administered within the 24 hours before **BSP retention tests**; or if they must, (e.g., for seizure control) the results be interpreted accordingly.

Phenobarbital can alter thyroid testing. Decreased total and free T4, normal T3, and either normal or increased TSH have been reported. It has been suggested to wait at least 4 weeks after discontinuing phenobarbital to perform thyroid testing.

In some dogs, phenobarbital may cause false positive **low dose dexamethasone suppression test**, by increasing the clearance of dexamethasone. Phenobarbital apparently has no effect on ACTH stimulation tests nor on the hormonal equilibrium of the adrenal axis.

**Dosages**

**Dogs**

For treatment of idiopathic epilepsy:

a) Initial oral dose: 2.5 mg/kg PO twice daily; to reach steady state levels faster may give an IV loading dose of 20 mg/kg. Adjust dosage based upon therapeutic levels, efficacy and adverse effects. (Podell 2000)

b) Perform CBC, Biochem profile and urology study. Initial dose: 2 (1-2.5) mg/kg q12h. Increase the dosage 50-100% in puppies due to their increased metabolic rate; adjust dosages based upon serum levels. (Quesnel 2000)

c) Initially, 2-4 mg/kg PO divided into 2-3 doses per day. If ineffective, may increase in a stepwise fashion to a maximum of 18-20 mg/kg/day (divided 2-3 times a day). Sudden discontinuation of the drug may result in seizures. (LeCouteur 1999)

For treatment of status epilepticus:

a) If seizures persist after diazepam therapy (2 or more seizures recur; or gross motor activity persists) give phenobarbital bolus of 2 - 5 mg/kg (can be repeated at 20 minute intervals, up to two times). Add phenobarb to diazepam infusion at a rate of 2 - 10 mg/hour. If seizures are sustained or high frequency seizures recur, consider pentobarbital coma. (Quesnel 2000)

For sedation:

a) 2.2 - 6.6 mg/kg PO bid (Walton 1986)

b) Treatment of irritable bowel syndrome: 2.2 mg/kg PO bid (Morgan 1988)

c) For adjunctive tx of compulsive behaviors: 2 - 20 mg/kg q12-24h (Line 2000)
Cats

Treatment of idiopathic epilepsy:
  a) Perform CBC, Biochem profile and urology study. Initial dose: 2 (1-2.5) mg/kg q12h. Increase the dosage 50-100 % possibly in kittens due to their increased metabolic rate; adjust dosages based upon serum levels. (Quesnel 2000)
  b) For status epilepticus: If seizures persist after diazepam therapy (2 or more seizures recur; or gross motor activity persists) give phenobarbital bolus of 2 - 5 mg/kg (can be repeated at 20 minute intervals, up to two times). Add phenobarb to diazepam infusion at a rate of 2 - 10 mg/hour. If seizures are sustained or high frequency seizures recur, consider pentobarbital coma.
For oral maintenance therapy: 1 - 2 mg/kg PO every 12 hours; adjust dosages based upon serum levels (Shell 2000)

Treatment of status epilepticus:
  a) 6 mg/kg IM or IV q6-12h as needed (Kirk 1986)

Sedation:
  a) For controlling excessive feline vocalization for situational distress (e.g., riding in automobiles): 2 - 3 mg/kg PO prn (Overall 2000)

Ferrets

a) 1 - 2 mg/kg PO 2-3 times daily (Williams 2000)

Cattle

For enzyme induction in organochlorine toxicity:
  a) 5 grams PO for 3-4 weeks, off 3-4 weeks, the repeat for 3-4 more weeks. (Smith 1986)

Horses

Note: ARCI UCGFS Class 2 Drug
  a) Loading dose of 12 mg/kg IV over 20 minutes, then 6.65 mg/kg IV over 20 minutes every 12 hours (Duran et al. 1987)
  b) 11 mg/kg PO q24 hours (Ravis et al. 1987)
  c) Foals; for seizures: 20 mg/kg diluted with normal saline to a volume of 30-35 ml infused over 25-30 minutes IV, then 9 mg/kg diluted and infused as above q8h. Recommend monitoring serum levels if possible. (Spehar et al. 1984)

MONITORING PARAMETERS
  1) Anticonvulsant (or sedative) efficacy
  2) Adverse effects (CNS related, PU/PD, weight gain)
  3) Serum phenobarbital levels if lack of efficacy or adverse reactions noted. Although there is some disagreement among clinicians, therapeutic serum levels in dogs are thought to mirror those in people (20 - 40 micrograms/ml). Therapeutic levels in cats may be closer to 10 - 30 mcg/ml. Animals on bromides and phenobarbital may require lower serum levels for seizure control.
  4) If used chronically, routine CBC's, liver enzymes (especially ALT & AST), and bilirubin at least every 6 months.

CLIENT INFORMATION
Compliance with therapy must be stressed to clients for successful epilepsy treatment. Encourage client to give doses at the same time each day. Keep medications out of reach of children and stored in child-resistant packaging. Veterinarian should be contacted if animal develops significant adverse reactions (including symptoms of anemia and/or liver disease) or seizure control is unacceptable.
**Dosage Forms/Preparations/FDA Approval Status/Withholding Times**

**Veterinary-Approved Products**

None

**Human-Approved Products**

Phenobarbital Tablets 15 mg, 16 mg, 30 mg, 60 mg, 90 mg, 100 mg; Solfoton® (ECR Pharm), generic; Capsules 16 mg, Solfoton® (ECR Pharm), (Rx; C-IV)

Phenobarbital Elixir 15 mg/5ml in pt and UD 5, 10 & 20 ml, 20 mg/5ml in pt, gal, UD 5 and 7.5 ml Generic; (Rx; C-IV)

Phenobarbital Sodium for Injection 30 mg/ml, 60 mg/ml, 65 mg/ml, 130 mg/ml; in 1 ml amps, Tubex and vials; Phenobarbital Sodium® (Wyeth-Ayerst); Luminal Sodium® (Sanofi Winthrop) Generic; (Rx; C-IV)

Also known as phenylethylmalonylurea or phenobarbitone. Other trade names may include: Luminal® (Winthrop-Breon), and Barbita® (Vortech). Phenobarbital is a **Class-IV controlled substance** and is available by prescription (Rx) only.

**Piroxicam**

**Prescriber Highlights**

- NSAID w/ antiinflammatory and antitumor (indirect) activity
- Contraindicated: Hypersensitivity or severely allergic to aspirin or other NSAIDs. Extreme caution: active, or a history of GI ulcer disease or bleeding disorders, cats. Caution: severely compromised cardiac function.
- Adverse effects: GI ulceration and bleeding, renal papillary necrosis, and peritonitis.
- Probably safer NSAIDs available for pain/inflammation for dogs and cats
- Drug Interactions; lab interactions

**Chemistry**

An oxicam derivative non-steroidal antiinflammatory agent, piroxicam occurs as a white, crystalline solid. It is sparingly soluble in water. Piroxicam is structurally not related to other non-steroidal antiinflammatory agents.

**Storage/Stability/Compatibility**

Capsules should be stored at temperatures less than 30°C in tight, light-resistant containers. When stored as recommended, capsules have an expiration date of 36 months after manufacture.

**Pharmacology**

Like other non-steroidal antiinflammatory agents, piroxicam has antiinflammatory, analgesic and antipyretic activity. The drug’s antiinflammatory activity is thought to be primarily due to its inhibition of prostaglandin synthesis, but additional mechanisms (e.g., superoxide formation inhibition) may be important. As with other NSAIDs, piroxicam can affect renal function, cause GI mucosal damage, and inhibit platelet aggregation.

Piroxicam's antitumor effects are believed to be due to its action on the immune system and not as a result of direct effects on tumor cells.
**USES/INDICATIONS**

In dogs, piroxicam may be beneficial in reducing the pain and inflammation associated with degenerative joint disease, but there are safer alternatives available. It's primary use is in dogs as adjunctive treatment of bladder transitional cell carcinoma. It may also be of benefit in squamous cell carcinomas, mammary adenocarcinoma, and transmissible venereal tumor (TVT).

**PHARMACOKINETICS**

After oral administration, piroxicam is well absorbed from the gut. While the presence of food will decrease the rate of absorption, it will not decrease the amount absorbed. It is not believed that antacids significantly affect absorption.

Piroxicam is highly bound to plasma proteins. In humans, synovial levels are about 40% of those found in the plasma. Maternal milk concentrations are only about 1% of plasma levels.

In humans, piroxicam has a very long plasma half-life (about 50 hours). The drug is principally excreted as metabolites in the urine after hepatic biotransformation.

**CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY**

Piroxicam is contraindicated in patients hypersensitive to it or who are severely allergic to aspirin or other NSAIDs. It should be used only when its potential benefits outweigh the risks in patients with active, or a history of GI ulcer disease or bleeding disorders. Because peripheral edema has been noted in some human patients, it should be used with caution in patients with severely compromised cardiac function.

Piroxicam has not been evaluated for use in cats. It must be used with extreme caution, if at all, in this species.

Animal studies have not demonstrated any teratogenic effects associated with piroxicam. The drug is excreted into milk in very low concentrations (about 1% found in maternal plasma).

**ADVERSE EFFECTS/WARNINGS**

Like other NSAIDs used in dogs, piroxicam has the potential for causing significant GI ulceration and bleeding. The therapeutic window for the drug is very narrow in dogs as doses as low as 1 mg/kg given daily have caused significant GI ulceration, renal papillary necrosis, and peritonitis. Other adverse effects reported in humans and potentially possible in dogs include CNS effects (headache, dizziness, etc.), otic effects (tinnitus), elevations in hepatic function tests, pruritus and rash, and peripheral edema. Renal papillary necrosis has been seen in dogs at post-mortem, but apparently clinical effects have not been noted with these occurrences.

**OVERDOSAGE/ACUTE TOXICITY**

There is limited information available, but dogs may be more sensitive to the drugs ulcerative effects than are humans. Patients ingesting significant overdoses should be monitored carefully and gut removal techniques employed when warranted. Treatment is supportive.

**DRUG INTERACTIONS**

Piroxicam may potentiate the renal toxicity of cisplatin when used in combination.

Because piroxicam is highly bound to plasma proteins, it can displace or be displaced by other highly protein bound drugs, including warfarin, phenylbutazone, etc.

Because piroxicam may inhibit platelet aggregation and also cause gastrointestinal ulceration, when used with other drugs that alter hemostasis (e.g., heparin, warfarin, etc.) and/or cause gastrointestinal erosion (e.g., aspirin, flunixin, phenylbutazone, corticosteroids, etc.), increased likelihood of bleeding or ulceration may occur.

NSAIDs (including piroxicam ) may potentially significantly reduce the excretion of methotrexate and cause toxicity.

**LABORATORY CONSIDERATIONS**

Piroxicam may cause falsely elevated blood glucose values when using the glucose oxidase and peroxidase method using ABTS as a chromogen.
DOSES

**Dogs**

As an adjunctive therapy of transitional cell carcinoma of the bladder:

a) 0.3 mg/kg PO once a day (Knapp, Richardson et al. 1994)

b) 0.3 mg/kg PO once a day. Give with food. Consider adding misoprostel at 3 mcg/kg PO q8h for dogs who tolerate NSAIDs poorly. Discontinue if severe irritation or ulceration occur. Treat ulcers and if signs abate, may resume piroxicam with misoprostel. (Frimberger 2000)

As an antiinflammatory/analgesic:

a) 0.3 mg/kg PO every other day (q48h) (Boothe 1992)
b) 0.3 mg/kg PO once daily, then once every other day in food (Hardie 2000)

**Cats**

As an adjunctive therapy of transitional cell carcinoma of the bladder:

a) The author has seen several anecdotal dosage recommendations. These generally fall into the: "0.3 mg/kg PO once a day to every other day with food" category. Use with caution as therapeutic window is very narrow. (Plumb)

**Rabbits/Rodents/Pocket Pets**

a) **Rabbits**: For fracture associated limb swelling: 0.1 - 0.2 mg/kg PO q8h for 3 weeks (Ivey and Morrisey 2000)

**MONITORING PARAMETERS**

1) Adverse Effects (particularly GI bleeding); 2) Liver function tests should be monitored occasionally with chronic use

**CLIENT INFORMATION**

Have clients monitor for GI ulceration/bleeding (anorexia, tarry stools, etc). Do not exceed dosage recommendations without veterinarian's approval. It has been suggested to give the drug with food to reduce GI upset potential.

**DOSEAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**

None

**Human-Approved Products**

Piroxicam Oral Capsules 10 mg, 20 mg; Feldene® (Pfizer); generic, (Rx)
**Propofol**

**Prescriber Highlights**
- Short-acting injectable hypnotic agent
- Contraindicated: hypersensitive to it or any of component of the product. Caution: severe stress or have undergone trauma, hypoproteinemia, hyperlipidemia, seizures or anaphylaxis history.
- Adverse effects: Transient respiratory depression is common but usually clinically tolerable. Apnea possible, esp. if given too rapidly. May cause histamine release, anaphylactoid rxns possible. Hypotension, seizure-like symptoms (paddling, opisthotonus, myoclonic twitching) during induction. Repeated doses in cats: increased Heinz body production, slowed recoveries, anorexia, lethargy, malaise, and diarrhea.
- Little if any analgesia provided.
- Consider dose reduction if using other CNS depressant
- Sufficient monitoring and patient-support capabilities mandatory
- Cat's with preexisting liver disease may be susceptible to longer recovery times.
- Drug Interactions

**Chemistry**
Propofol is an alkylphenol derivative (2,6-diisopropylphenol). The commercially available injection is an emulsion containing 100 mg/ml of soybean oil, 22.5 mg/ml of glycerol, and 12 mg/ml of egg lecithin. The emulsion has a pH of 7-8.5. Propofol may also be known as disoprofol.

**Storage/Stability/Compatibility**
Store propofol injection below 22°C (72°F), but not below 4°C (40°F); do not refrigerate or freeze. Protect from light. Shake well before using. Do not use if the emulsion has separated. The manufacturer recommends discarding any unused portion at the end of the anesthetic procedure or after 6 hours, whichever occurs sooner.

Compatibility with other agents has not been well established. Propofol is physically compatible with the commonly used IV solutions (e.g., LRS, D5W) when injected into a running IV line.

**Pharmacology**
Propofol is a short acting hypnotic unrelated to other general anesthetic agents. Its mechanism of action is not well understood.

In dogs, propofol produces rapid, yet smooth and excitement-free anesthesia induction (in 30-60 seconds) when given slowly IV. Sub-anesthetic dosages will produce sedation, restraint and an unawareness of surroundings. Anesthetic dosages produce unconsciousness and good muscle relaxation.

Propofol’s cardiovascular effects include arterial hypotension, bradycardia, (especially in combination with opiate premedicants) and negative inotropism. It causes significant respiratory depression, particularly with rapid administration or very high dosages. Propofol also decreases intraocular pressure, increases appetite and has antiemetic properties. It does not appear to precipitate malignant hyperthermia and it has little or no analgesic properties.

**Uses/Indications**
In appropriate patients, propofol may be useful as an induction agent (especially before endotracheal intubation or an inhalant anesthetic); as an anesthetic for outpatient diagnostic or minor procedures (e.g., laceration repair, radiologic procedures, minor dentistry, minor biopsies, endoscopy, etc.); and as a treatment for refractory status epilepticus. Propofol may be of particular usefulness for use in Greyhounds and in patients with preexisting cardiac dysrhythmias.

Propofol may be safely used in animals with liver or renal disease and in animals with mild to moderate cardiac disease.

In dogs, propofol's labeled indications are: 1) for induction of anesthesia; 2) for maintenance of anesthesia for up to 20 minutes; 3) for induction of general anesthesia where maintenance is provided by inhalant anesthetics.
**PHARMACOKINETICS**

After IV administration, propofol rapidly crosses the blood brain barrier and has an onset of action usually within one minute. Duration of action after a single bolus lasts about 2-5 minutes. It is highly bound to plasma proteins (95-99%), crosses the placenta, is highly lipophilic and reportedly enters maternal milk.

Propofol’s short duration of action is principally due to its rapid redistribution from the CNS to other tissues. It is rapidly biotransformed in the liver via glucuronide conjugation to inactive metabolites which are then excreted primarily by the kidneys. Because cat’s do not glucuronidate as well as dogs or humans, this may help explain their problems with consecutive day administration (see Adverse Effects below).

There are limited data available on propofol’s pharmacokinetic parameters in dogs. The steady state volume of distribution is >3L/kg, elimination half life is about 1.4 hours and clearance is about 50 ml/kg/min.

**CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY**

Propofol is contraindicated in patients hypersensitive to it or any of component of the product. It should not be used in patients where general anesthesia or sedation are contraindicated. Propofol should only be used in facilities where sufficient monitoring and patient-support capabilities are available.

Because patients who are in shock, under severe stress or have undergone trauma may be overly sensitive to the cardiovascular and respiratory depressant effects of propofol, it should be used with caution in these patients. Adequate perfusion should be maintained before and during propofol anesthesia and dosage adjustments may be necessary.

Because propofol is so highly bound to plasma proteins, patients with hypoproteinemia may be susceptible to untoward effects. Other general anesthetic agents may be a safer choice in these patients.

The benefits of propofol should be weighed against its risks in patients with a history of hyperlipidemia, seizures or anaphylactic reactions. Cat’s with preexisting liver disease may be susceptible to longer recovery times.

Propofol crosses the placenta and its safe use during pregnancy has not been established. High dosages (6 times those recommended) in laboratory animals caused increased maternal death and decreased offspring survival rates after birth.

**ADVERSE EFFECTS/WARNINGS**

Transient respiratory depression is common but is usually clinically tolerable. But there is a relatively high incidence of apnea with resultant cyanosis if propofol is given too rapidly, it should be given slowly (25% of the calculated dose every 30 seconds until desired effect). Treat with assisted ventilation until spontaneous ventilation resumes.

Propofol has been documented to cause histamine release in some patients and anaphylactoid reactions (rare) have been noted in humans. Propofol has direct myocardial depressant properties and resultant arterial hypotension has been reported.

Occasionally, dogs may exhibit seizure-like symptoms (paddling, opisthotonus, myoclonic twitching) during induction, which if persist, may be treated with intravenous diazepam. Propofol may have both anticonvulsant and seizure-causing properties. It should be used with caution in patients with a history of, or active seizure disorders. However, some clinicians believe that propofol is actually better-suited to use in seizure patients or in high seizure-risk procedures (e.g., myelography) than is thiopental.

While propofol is not inexpensive, it should ideally be used in a single-use fashion as it is a good growth medium (contains no preservative) for bacteria.

When used in combination with other CNS depressant premedicants (e.g., acepromazine, narcotics, diazepam, etc.), a decrease in dosage of about 25% (from the single agent dose) should be considered. In very thin animals, consider dosage reduction as well.

When used repeatedly (once daily) in cats, increased Heinz body production, slowed recoveries, anorexia, lethargy, malaise, and diarrhea have been noted. Heinz body formation is due to oxidative injury to RBC’s and has been documented in cats with other phenolic compounds as well. Consecutive use in dogs appears to be safe.

Pain upon injection has been reported in humans, but does not appear to be of major significance for dogs or cats. Extravasation of injection is not irritating nor does it cause tissue sloughing.
Propofol does not provide good analgesia, so appropriate analgesic agents should be used before and after painful procedures.

**Overdosage/Acute Toxicity**

Overdosages are likely to cause significant respiratory depression and potentially cardiovascular depression. Treatment should consist of propofol discontinuation, artificial ventilation with oxygen, and if necessary, symptomatic and supportive treatment for cardiovascular depression (e.g., intravenous fluids, pressors, anticholinergics, etc.).

**Drug Interactions**

Propofol used in conjunction with preanesthetic agents (e.g., acepromazine, opiates) may cause increased vasodilation and negative cardiac inotropy. This may be of particular concern in animals with preexisting cardiopulmonary disease, in shock, or suffering from trauma.

Propofol-induced bradycardia may be exacerbated in animals receiving opiate premedicants, particularly when anticholinergic agents (e.g., atropine) are not given concurrently.

As would be logically expected, increased CNS depressant effects and recovery times may be noted in patients receiving other CNS depressant medications with propofol.

**Drugs that inhibit the hepatic P-450 enzyme system (e.g., chloramphenicol, cimetidine) or other basic lipophilic drugs (e.g., fentanyl, halothane)** may potentially increase the recovery times associated with propofol. Clinical significance is unclear, but in cats it may be of significance.

**Doses**

**Dogs & Cats**

Note: The Rapinovet® (Schering-Plough) package insert has very detailed dosing recommendations for both induction and maintenance of general anesthesia with propofol, including dosage adjustments when acepromazine, xylazine, butorphanol, oxymorphone or medetomidine premedication is used.

As an anesthetic:

a) As a single injection (25% of the calculated dose every 30 seconds until desired effect):

For healthy, unpremedicated animal: 6 mg/kg IV

For healthy, premedicated animal: After tranquilizer (e.g., acepromazine) = 4 mg/kg IV; After sedative (e.g., xylazine, opioids) = 3 mg/kg IV

As a constant infusion:

For sedation only: 0.1 mg/kg/minute

For minor surgery: 0.6 mg/kg/min, or 1 ml (10 mg) per minute per 12-25 kg of body weight (Robinson, Sanderson et al. 1993)

b) Dogs: For induction without premedication: 5 - 6 mg/kg IV

With acepromazine (0.05 mg/kg IM, IV, or SC), propofol given at 3-4 mg/kg IV

With acepromazine and oxymorphone (0.09 mg/kg IM, IV or SC), propofol given at 2.3 mg/kg IV. Xylazine or medetomidine premeds may reduce propofol dose further.

Cats: Premed with acepromazine (0.05 - 1 mg/kg IM) with or without an analgesic such as butorphanol (0.2 - 0.4 mg/kg IM) and induce with propofol at 4 - 6 mg/kg IV. Doses of propofol at 8-13 mg/kg IV will allow intubation without topical anesthesia, lower propofol dose if topical anesthesia is used. (Mathews 1999)

c) 6 mg/kg IV; in healthy animals 25% of the calculated dose is administered every 30 seconds until intubation is possible. After induction, duration of anesthesia is only 2.5 - 9.4 minutes. Maintenance anesthesia obtained using either inhalational agents or a continuous infusion of propofol at approximately 0.4 mg/kg/minute. If anesthesia appears inadequate, a small bolus of 1 mg/kg followed by an increase in the infusion rate by 25%. If infusion is too deep, discontinue infusion until suitable anesthesia level is achieved. An infusion dose of 0.1 mg/kg/min appears to be suitable dose for sedation in the dog. (Ilkiw 1992)
d) As an induction agent for halothane or isoflurane anesthesia: 6.6 mg/kg IV given over 60 seconds to unpremedicated dogs. Best achieved by early intubation and administration of the inhalant following propofol induction. (Bufalari, Miller et al. 1998)

For refractory status epilepticus:
  a) Using IV bolus or constant rate IV infusion: 0.1 - 0.6 mg/kg/minute. Use only in settings where definitive airway control and hemodynamic support can occur.(Platt and McDonnell 2000)

**Rabbits/Rodents/Pocket Pets**
  a) **Rabbits**: 5 - 14 mg/kg slow IV (20 mg/kg/minute) to effect; not recommended as the sole agent for maintenance (Ivey and Morrisey 2000)
  b) **Mice**: 26 mg/kg IV. **Rats**: 10 mg/kg IV (Adamcak and Otten 2000)

**Reptiles**
  a) Iguanas: 3 mg/kg IV via either intraosseous catheter or into the coccygeal or ventral abdominal vein. Wait 3-5 minutes before giving additional increments. May also be used in tortoises. (Heard 1999)

**MONITORING PARAMETERS**
1) Level of anesthesia/CNS effects; 2) Respiratory depression;
3) Cardiovascular status (cardiac rate/rhythm; blood pressure)

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**
  Propofol Injectable 10 mg/ml in 20 ml (single use) vials; **Rapinovet®** (Schering Plough); **PropoFlo®**(Abbott) (Rx). Approved for use in dogs and cats.

**Human-Approved Products**
  Propofol Injection 10 mg/ml in 20 ml ampules and 50 & 100 ml vials for infusion; **Diprivan®** (Zeneca); (Rx)

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**SEVOFLURANE**

**PRESCRIBER HIGHLIGHTS**
  - Inhalational anesthetic similar to isoflurane, but more rapid induction and recovery
  - Currently more expensive than isoflurane
  - Drug-drug interactions

**CHEMISTRY**
An isopropyl ether inhalational anesthetic with a molecular wt. of 200, saturate vapor pressure at 20°C of 160 mmHg and a boiling pt. of 58.5°C. It is reported to have a pleasant odor and is not irritating to airways. It is non-flammable and non-explosive. It is clear, colorless liquid that is miscible with ethanol or ether and slightly soluble in water.

**STORAGE/StABILITY/COMPATIBILITY**
Sevoflurane should be stored at room temperature. Sevoflurane does not react with metal.

**PHARMACOLOGY**
While the precise mechanism that inhalent anesthetics exert their general anesthetic effects is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Sevoflurane has a very low blood:gas partition coefficient (0.6) allowing very rapid anesthesia induction and recovery. Rapid mask induction is possible.
Pharmacologic effects of sevoflurane are similar to isoflurane and include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression, hypotension, vasodilatation, and myocardial depression (less so than with halothane) and muscular relaxation.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for sevoflurane in various species: Dog = 2.09 - 2.4; Cat = 2.58; Horse = 2.31; Sheep = 3.3; Swine = 1.97-2.66; Human (adult) = 1.71 - 2.05. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).

**USES/INDICATIONS**
Sevoflurane may be useful in a variety of species when rapid induction and/or rapid recoveries are desired with an inhalational anesthetic.

**PHARMACOKINETICS**
Because of its low solubility in blood, only small concentrations of sevoflurane in the blood are required to be dissolved in blood before alveolar partial pressures are in equilibrium with arterial partial pressures. This low solubility also means that sevoflurane is rapidly removed from the lungs. It is unknown what percent sevoflurane is bound to plasma proteins. The majority of sevoflurane is excreted via the lungs, but about 3% is metabolized in the liver via the cytochrome P450 2E1 isoenzyme system.

**CONTRAINDICATIONS/PRECAUTIONS/REPRODUCTIVE SAFETY**
Sevoflurane is contraindicated in patients with a history or predilection towards malignant hyperthermia. It should be used with caution (benefits vs. risks) in patients with increased CSF or head injury, or renal insufficiency.

Because of its rapid action, use caution not to overdose during the induction phase. Because of the rapid recovery associated with sevoflurane use caution (and appropriate sedation during the recovery phase), particularly with large animals.

Geriatric animals may require less inhalation anesthetic.

Sevoflurane does not appear to be a good inhalational anesthetic in rabbits (breath holding, struggling).

No overt fetotoxicity or teratogenicity has been demonstrated in lab animal studies, but definite safety has not been established for use during pregnancy.

**ADVERSE EFFECTS/WARNINGS**
Seems to be well tolerated. Hypotension may occur and is considered to be dose related. Dose-dependent respiratory depression, and GI effects (nausea, vomiting, ileus) have been reported. While cardiodepression generally is minimal at doses causing surgical planes of anesthesia, it may occur; bradycardia is possible.

Malignant hyperthermia may be triggered by this agent (like other inhalational anesthetics).

Sevoflurane can react with carbon dioxide absorbents to produce "compound A", a nephrotoxin. However, after extensive clinical use in humans, nephrotoxicity has not been demonstrated to be of clinical concern.

Sevoflurane should be used in precision, agent-specific, out of circuit vaporizers.

**OVERDOSE/AcUTE TOXICITY**
In the event of an overdosage, discontinue sevoflurane, maintain airway and support respiratory and cardiac function as necessary.

**DRUG INTERACTIONS**
While sevoflurane sensitizes the myocardium to the effects of sympathomimetics less so than halothane, arrhythmias may still result. Drugs included are: dopamine, epinephrine, norepinephrine, ephedrine, metaraminol, etc. Caution and monitoring is advised.

Non-depolarizing neuromuscular blocking agents, systemic aminoglycosides, systemic lincomycins should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur.
Concomitant administration of **succinylcholine** with inhalation anesthetics may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia as well.

**LABORATORY CONSIDERATIONS**
Inhalational anesthetics may cause transient increases in liver function tests, WBC's and glucose.

**DOSES**
Most recommendations are for 2 to 2.5 MAC for induction (for species values see pharmacology above) and 1 to 1.5 MAC for maintenance.

**MONITORING PARAMETERS**
1) Respiratory and ventilatory status; 2) Cardiac rate/rhythm; blood pressure (particularly with "at risk" patients; 3) Level of anesthesia

**DOSAGE FORMS/PREPARATIONS/FDA APPROVAL STATUS/WITHHOLDING TIMES**

**Veterinary-Approved Products**
Sevoflurane in 250 ml btls; *SevoFlo®* (Abbott); (Rx)

**Human-Approved Products**
Sevoflurane in 250 ml btls; *Ultane®* (Abbott); (Rx)

**THIOPENTAL SODIUM**

**PRESCRIBER HIGHLIGHTS**
- Ultra-short acting thiobarbiturate used for anesthesia induction, or for anesthesia for very short procedures
- Contraindicated: Absolute contraindications: absence of suitable veins for IV administration, history of hypersensitivity reactions to barbiturates, status asthmaticus. Relative contraindications: severe cardiovascular disease or preexisting ventricular arrhythmias, shock, increased intracranial pressure, myasthenia gravis, asthma, and conditions where hypnotic effects may be prolonged (e.g., severe hepatic disease, myxedema, severe anemia, excessive premedication, etc). Greyhounds (and other sight hounds) metabolize thiobarbts much more slowly than other breeds, consider using methohexital instead. Horses: preexisting leukopenia; thiopental alone may cause excessive ataxia and excitement.
- Avoid extravasation, intra-carotid or intra-arterial injections or use of concentrations of less than 2% in sterile water. Too rapid IV administration can cause significant vascular dilatation and hypoglycemia.
- Adverse effects: Dogs: ventricular bigeminy Cats: apnea after injection, mild arterial hypotension. Horses: excitement and severe ataxia (if used alone); transient leukopenias, hyperglycemia, apnea, moderate tachycardia, mild respiratory acidosis
- Severe CNS toxicity and tissue damage has resulted in horses receiving intra-carotid injections of thiobarbiturates.
- C-III controlled substance
- Drug Interactions

**CHEMISTRY**
A thiobarbiturate, thiopental occurs as a bitter-tasting, white to off-white, crystalline powder or a yellow-white hygroscopic powder. It is soluble in water (1 gram in 1.5 ml) and alcohol. Thiopental has a pKₘ of 7.6 and is a weak organic acid.
STORAGE/Stability/Compatibility
When stored in the dry form, thiopental sodium is stable indefinitely. Thiopental should be diluted with only sterile water for injection, sodium chloride injection, or D5W. Concentrations of less than 2% in sterile water should not be used as they may cause hemolysis. After reconstitution, solutions are stable for 3 days at room temperature and for 7 days if refrigerated.

However, as no preservative is present, it is recommended it be used within 24 hours after reconstitution. After 48 hours, the solution has been reported to attack the glass bottles it is stored in. Thiopental may also adsorb to plastic IV tubing and bags. Do not administer any solution that has a visible precipitate.

The following agents have been reported to be physically compatible when mixed with thiopental: aminophylline, chloramphenicol sodium succinate, hyaluronidase, hydrocortisone sodium succinate, neostigmine methysulfate, oxytocin, pentobarbital sodium, phenobarbital sodium, potassium chloride, scopolamine HBr, sodium iodide, and tubocurarine chloride (recommendations conflict with regard to tubocurarine; some clinicians recommend not mixing with thiopental).

The following agents have been reported to be physically incompatible when mixed with thiopental: Ringer's injection, Ringer's injection lactate, amikacin sulfate, atropine sulfate, benzquinamide, cephapirin sodium, chlorpromazine, codeine phosphate, dimenhydrinate, diphenhydramine, ephedrine sulfate, glycopyrrolate, hydromorphone, insulin (regular), levorphanol bitartrate, meperidine, metaraminol, morphine sulfate, norepinephrine bitartrate, penicillin G potassium, prochlorperazine edisylate, promazine HCl, promethazine HCl, succinylcholine chloride, and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (e.g., Handbook on Injectable Drugs by Trissel; see bibliography).

PHarmacology
Because of their high lipid solubility, thiobarbiturates rapidly enter the CNS and produce profound hypnosis and anesthesia. They are also known as ultrashort-acting barbiturates. See the monograph: Barbiturates, Pharmacology of, for additional information.

Uses/Indications
Because of their rapid action and short duration, the thiobarbiturates are excellent induction agents for general anesthesia with other anesthetics or as the sole anesthetic agent for very short procedures.

Pharmacokinetics
Following IV injection of therapeutic doses, hypnosis and anesthesia occur within one minute. The drug rapidly enters the CNS and then redistributes to muscle and adipose tissue in the body. The short duration of action of these agents is due less to rapid metabolism than to this redistribution out of the CNS and into muscle and fat stores. Greyhounds and other sight hounds may exhibit longer recovery times than other breeds. This may be due to these breeds low body fat levels or differences in the metabolic handling of the thiobarbiturates.

Thiopental is metabolized by the hepatic microsomal system and several metabolites have been isolated. The elimination half-life in dogs has been reported as being approximately 7 hours and in sheep, 3-4 hours. Very little of the drug is excreted unchanged in the urine (0.3% in humans), so dosage adjustments are not necessary in patients with chronic renal failure.

Contraindications/Precautions
The following are considered to be absolute contraindications to the use of thiopental: absence of suitable veins for IV administration, history of hypersensitivity reactions to the barbiturates, and status asthmaticus. Relative contraindications include: severe cardiovascular disease or preexisting ventricular arrhythmias, shock, increased intracranial pressure, myasthenia gravis, asthma, and conditions where hypnotic effects may be prolonged (e.g., severe hepatic disease, myxedema, severe anemia, excessive premedication, etc). These relative contraindications do not preclude the use of thiopental, but dosage adjustments must be considered and the drug must be given slowly and cautiously.

Because greyhounds (and other sight hounds) metabolize thiobarbiturates much more slowly than methohexital, many clinicians recommend using methohexital instead.
Thiopental readily crosses the placental barrier and should be used with caution during pregnancy.

In horses, thiopental should not be used if the patient has preexisting leukopenia. Some clinicians feel that thiopental should not be used alone in the horse as it may cause excessive ataxia and excitement.

Concentrations of less than 2% in sterile water should not be used as they may cause hemolysis. Extravasation and intra-arterial injections should be avoided because of the high alkalinity of the solution. Severe CNS toxicity and tissue damage has resulted in horses receiving intra-carotid injections of thiobarbiturates.

ADVERSE EFFECTS/Warnings
In dogs, thiopental has an approximate arrhythmogenic incidence of 40%. Ventricular bigeminy is the most common arrhythmia seen and is usually transient and generally responds to additional oxygen. Administration of catecholamines may augment the arrhythmogenic effects of the thiobarbiturates, while lidocaine may inhibit it. Cardiac output may also be reduced, but is probably only clinically significant in patients experiencing heart failure.

Cats are susceptible to developing apnea after injection and may also develop a mild arterial hypotension.

Horses can exhibit symptoms of excitement and severe ataxia during the recovery period if the drug is used alone. Horses also can develop transient leukopenias and hyperglycemia after administration. A period of apnea and moderate tachycardia and a mild respiratory acidosis may also develop after dosing.

Too rapid IV administration can cause significant vascular dilatation and hypoglycemia. Repeated administration of thiopental is not advised as recovery times can become significantly prolonged. Parasympathetic side effects (e.g., salivation, bradycardia) may be managed with the use of anticholinergic agents (atropine, glycopyrrolate).

OVERDOSAGE
Treatment of thiobarbiturate overdose consists of supporting respirations (O2, mechanical ventilation) and giving cardiovascular support (do not use catecholamines, e.g., epinephrine, etc).

DRUG INTERACTIONS
A fatal interaction has been reported in a dog receiving the proprietary product, Diathal® (procaine penicillin G, dihydrostreptomycin sulfate, diphenamid methylsulfate, and chlorpheniramine maleate) and the related compound thiamylal. Avoid using thiopental with this product.

The ventricular fibrillatory effects of epinephrine and norepinephrine are potentiated when used with thiobarbiturates and halothane.

CNS and respiratory depressant effects of CNS depressants (narcotics, phenothiazines, antihistamines, etc.) may be enhanced by thiobarbiturate administration.

Thiopental with furosemide may cause or increase postural hypotension. Sulfisoxazole IV has been shown to compete with thiopental at plasma protein binding sites. This may also occur with other sulfonamides.

DOSES
Note: Atropine sulfate or glycopyrrolate are often administered prior to thiobarbiturate anesthesia to prevent parasympathetic side effects. Some clinicians question, however, whether routine administration of the anticholinergic agents are necessary.

Thiobarbiturates are administered strictly to effect; doses are guidelines only.

Dogs
a) 13.2 - 26.4 mg/kg IV depending on duration of anesthesia required. (Pentothal® package insert- Ceva Laboratories)
b) 15 - 17 mg/kg IV for brief (7-10 minutes) anesthesia; 18 - 22 mg/kg IV for moderate (10-15 minutes) duration; 22 - 29 mg/kg IV for longer (15-25 minutes) duration (Booth 1988a)
c) 22 mg/kg IV; or 15.4 mg/kg IV after tranquilization; or 11 mg/kg IV after narcotic premedication. (Mandsager 1988)
Cats

a) 13.2 - 26.4 mg/kg IV depending on duration of anesthesia required. (Pentothal® package insert, Ceva Laboratories)
b) 22 mg/kg IV; or 15.4 mg/kg IV after tranquilization; or 11 mg/kg IV after narcotic premedication. (Mandsager 1988)

Rabbits/Rodents/Pocket Pets

a) Rabbits: 15 - 30 mg/kg IV to effect (Ivey and Morrisey 2000)
b) For chemical restraint:
   Mice: 50 mg/kg IP
   Rats: 40 mg/kg IP
   Hamsters/Gerbils: 30 - 40 mg/kg IP
   Guinea pig: 15 - 30 mg/kg IV
   Rabbits: 15 - 30 mg/kg IV (Burke 1999)

Cattle

a) Cattle: 8.14 - 15.4 mg/kg IV;
   For unweaned calves from which food has been withheld for 6-12 hours: no more than 6.6 mg/kg IV for deep surgical anesthesia. (Pentothal® package insert; Ceva Laboratories)
b) For calves under 2 weeks of age: 15 - 22 mg/kg IV slowly until complete muscular relaxation takes place, duration of anesthesia usually lasts 10-12 minutes. (Booth 1988a)
c) 5.5 mg/kg IV after sedation and administration with guaifenesin; or 8.8-11 mg/kg IV after tranquilization. (Mandsager 1988)

Horses

Note: ARCI UCGFS Class 2 Drug

a) With preanesthetic tranquilization: 6 - 12 mg/kg IV (an average of 8.25 mg/kg is recommended); Without preanesthetic tranquilization: 8.8-15.4 mg/kg IV (an average horse: 9.9 - 11 mg/kg IV) (Pentothal® package insert; Ceva Laboratories)
b) One gram of thiopental per 90 kg body weight as a 10% solution given evenly over 20 seconds 15 minutes after premedication with either 0.22 mg/kg IV xylazine or 0.05 mg/kg IV acepromazine. (Booth 1988a)
c) 5.5 mg/kg IV after sedation and administration with guaifenesin; or 8.8 - 11 mg/kg IV after tranquilization. (Mandsager 1988)

Swine

a) 5.5 - 11 mg/kg IV (Pentothal® package insert, Ceva Laboratories)
b) For swine weighing 5 - 50 kg: 10 - 11 mg/kg IV (Booth 1988a)

Sheep:

a) 9.9 - 15 mg/kg IV depending on depth of anesthesia required (Pentothal® package insert, Ceva Laboratories)

Goats

a) 20 - 22 mg/kg IV after atropine (0.7 mg/kg) IM (Booth 1988a)

Monitoring Parameters

1) Level of hypnosis/anesthesia
2) Respiratory status; cardiac status (rate/rhythm/blood pressure)

Client Information
This drug should only be used by professionals familiar with its effects in a setting where adequate respiratory support can be performed.

**Dosage Forms/Preparations**

**Veterinary-Approved Products:** None

Thiopental Sodium Powder for Injection: 5 g in 200 ml (reconstituted concentration = 2.5%) & 100 ml (reconstituted concentration = 5%). For small & large animal general anesthesia. *Pentothal® Sterile Powder* (Abbott) (CIII)

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**Xylazine HCl**

**Prescriber Highlights**

- Alpha₂-adrenergic agonist used for its sedative and analgesic in a variety of species. Sometimes used as an emetic in cats.
- Contraindicated: animals receiving epinephrine or having active ventricular arrhythmias. Extreme caution: preexisting cardiac dysfunction, hypotension or shock, respiratory dysfunction, severe hepatic or renal insufficiency, preexisting seizure disorders, or if severely debilitated. Should generally not be used in the last trimester of pregnancy, particularly in cattle. Do not give to ruminants that are dehydrated, have urinary tract obstruction, or are debilitated. Horses may kick after a stimulatory event (usually auditory); use caution. Avoid intra-arterial injection; may cause severe seizures and collapse. Caution in patients treated for intestinal impactions. Use cautiously in horses during the vasoconstrictive development phase of laminitis.
- Adverse effects **cats:** emesis, muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli and increased urination.
- Adverse effects **dogs:** muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, emesis, bloat from aerophagia which may require decompression.
- Adverse effects **horses:** muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, sweating, increased intracranial pressure or decreased mucociliary clearance.
- Adverse effects **cattle:** salivation, ruminal atony, bloating, regurgitation, hypothermia, diarrhea, bradycardia, premature parturition and ataxia.
- Yohimbine, atipamezole and tolazoline may be used alone or in combination to reverse effects or speed recovery times
- Dosages between species can be very different; be certain of product concentration when drawing up into syringe, especially if treating ruminants
- Drug Interactions

**Chemistry**

Xylazine HCl is a alpha₂-adrenergic agonist structurally related to clonidine. The pH of the commercially prepared injections is approximately 5.5. Dosages and bottle concentrations are expressed in terms of the base.

**Storage/Stability/Compatibility**

Do not store above 30°C (86°F). Xylazine is reportedly physically compatible in the same syringe with several compounds, including: acepromazine, buprenorphine, butorphanol, chloral hydrate, and meperidine.

**Pharmacology**

A potent alpha₂-adrenergic agonist, xylazine is classified as a sedative/analgesic with muscle relaxant properties. Although xylazine possesses several of the same pharmacologic actions as morphine, it does not cause CNS excitation in cats, horses or cattle, but causes sedation and CNS depression. In horses, the visceral analgesia produced has been demonstrated to be superior to that produced by meperidine, butorphanol or pentazocine.
Xylazine causes skeletal muscle relaxation through central mediated pathways. Emesis is often seen in cats, and is also seen occasionally in dogs receiving xylazine. While thought to be centrally mediated, neither dopaminergic blockers (e.g., phenothiazines) or alpha-blockers (yohimbine, tolazoline) block the emetic effect. Xylazine does not cause emesis in horses, cattle, sheep or goats. Xylazine depresses thermoregulatory mechanisms and either hypothermia or hyperthermia is a possibility depending on ambient air temperatures.

Effects on the cardiovascular system include an initial increase in total peripheral resistance with increased blood pressure followed by a longer period of lowered blood pressures (below baseline). A bradycardic effect can be seen with some animals developing a second degree heart block or other arrhythmias. An overall decrease in cardiac output of up to 30% may be seen. Xylazine has been demonstrated to enhance the arrhythmogenic effects of epinephrine in dogs with or without concurrent halothane.

Xylazine's effects on respiratory function are usually clinically insignificant, but at high dosages, it can cause respiratory depression with decreased tidal volumes and respiratory rates and an overall decreased minute volume. Brachycephalic dogs and horses with upper airway disease may develop dyspnea.

Xylazine can induce increases in blood glucose secondary to decreased serum levels of insulin. In non-diabetic animals, there appears to be little clinical significance associated with this effect.

In horses, sedatory signs include a lowering of the head with relaxed facial muscles and drooping of the lower lip. The retractor muscle is relaxed in male horses, but unlike acepromazine, no reports of permanent penile paralysis has been reported. Although, the animal may appear to be thoroughly sedated, auditory stimuli may provoke arousal with kicking and avoidance responses.

With regard to the sensitivity of species to xylazine definite differences are seen. Ruminants are extremely sensitive to xylazine when compared with horses, dogs, or cats. Ruminants generally require approximately $1/10^5$ the dosage that is required for horses to exhibit the same effect. In cattle (and occasionally cats and horses), polyuria is seen following xylazine administration, probably as a result of decreased production of vasopressin (anti-diuretic hormone, ADH). Bradycardia and hypersalivation are also seen in cattle and are diminished by pretreating with atropine. Swine, require 20-30 times the ruminant dose and therefore, xylazine is not routinely used in this species.

**Uses/indications**

Xylazine is approved for use in dogs, cats, horses, deer, and elk. It is indicated in dogs, cats and horses to produce a state of sedation with a shorter period of analgesia, and as a preanesthetic before local or general anesthesia. Because of the emetic action of xylazine in cats, it is occasionally used to induce vomiting after ingesting toxins.

**Pharmacokinetics**

Absorption is rapid following IM injection, but bioavailabilities are incomplete and variable. Bioavailabilities of 40-48% in the horse, 17-73% in the sheep, and 52-90% in the dog have been reported after IM administration.

In horses, the onset of action following IV dosage occurs within 1-2 minutes with a maximum effect 3-10 minutes after injection. The duration of effect is dose dependent but may last for approximately 1.5 hours. The serum half-life after a single dose of xylazine is approximately 50 minutes in the horse and recovery times generally take from 2-3 hours.

In dogs and cats, the onset of action following an IM or SC dose is approximately 10-15 minutes, and 3-5 minutes following an IV dose. The analgesic effects may persist for only 15-30 minutes, but the sedative actions may last for 1-2 hours depending on the dose given. The serum half-life of xylazine in dogs has been reported as averaging 30 minutes. Complete recovery after dosing may take from 2-4 hours in dogs and cats.

Xylazine is not detected in milk of lactating dairy cattle at 5 & 21 hours post-dose, but the FDA has not approved the use of this agent in dairy cattle and no meat or milk withdrawal times have been specified.

**Contraindications/precautions**

Xylazine is contraindicated in animals receiving epinephrine or having active ventricular arrhythmias. It should be used with extreme caution in animals with preexisting cardiac dysfunction, hypotension or shock, respiratory dysfunction, severe hepatic or renal insufficiency, preexisting seizure disorders, or if
severely debilitated. Because it may induce premature parturition, it should generally not be used in the last trimester of pregnancy, particularly in cattle.

Be certain of product concentration when drawing up into syringe, especially if treating ruminants. Do not give to ruminants that are dehydrated, have urinary tract obstruction, or are debilitated. It is not approved for any species to be consumed for food purposes.

Horses have been known to kick after a stimulatory event (usually auditory); use caution. The addition of opioids (e.g., butorphanol) may help temper this effect, but may cause increased risks for hypotension or ileus development. Avoid intra-arterial injection; may cause severe seizures and collapse. The manufacturers warn against using in conjunction with other tranquilizers. Because this drug may inhibit gastrointestinal motility use with caution in patients treated for intestinal impactions. Use cautiously in horses during the vasoconstrictive development phase of laminitis as xylazine has been shown to reduce digital flow of blood for about 8 hours after administration.

**ADVERSE EFFECTS/WARNINGS**

Emesis is generally seen within 3-5 minutes after xylazine administration in cats and occasionally in dogs. To prevent aspiration, do not induce further anesthesia until this time period has lapsed. Other adverse effects listed in the package insert (Gemini®, Butler) for dogs and cats include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and increased urination in cats.

Dogs may develop bloat from aerophagia which may require decompression. Because of gaseous distention of the stomach, xylazine's use before radiography can make test interpretation difficult.

Adverse effects listed in the package insert (AnaSed®, Lloyd) for horses include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and sweating (rarely profuse). Additionally, horses may develop increased intracranial pressure or decreased mucociliary clearance rates when xylazine is used.

Adverse reactions reported in cattle include salivation, ruminal atony, bloating and regurgitation, hypothermia, diarrhea, and bradycardia. The hypersalivation and bradycardia may be alleviated by pretreating with atropine. Xylazine may induce premature parturition in cattle.

Large animals may become ataxic following dosing and caution should be observed.

**OVERDOSAGE**

In the event of an accidental overdosage, cardiac arrhythmias, hypotension, and profound CNS and respiratory depression may occur. Seizures have also been reported after overdoses. There has been much interest in using alpha-blocking agents as antidotes or reversal agents to xylazine. Yohimbine, atipamezole and tolazoline have been suggested to be used alone and in combination to reverse the effects of xylazine or speed recovery times. Separate monographs for yohimbine and atipamezole are available with suggested doses, etc.

To treat the respiratory depressant effects of xylazine toxicity, mechanical respiratory support with respiratory stimulants (e.g., doxapram) have been recommended for use.

**DRUG INTERACTIONS**

The use of epinephrine with & without the concurrent use of halothane concomitantly with xylazine may induce the development of ventricular arrhythmias.

The combination use of acepromazine with xylazine is generally considered to be safe, but there is potential for additive hypotensive effects and this combination should be used cautiously in animals susceptible to hemodynamic complications.

Other CNS depressant agents (barbiturates, narcotics, anesthetics, phenothiazines, etc.) may cause additive CNS depression if used with xylazine. Dosages of these agents may need to be reduced.

A case report of a horse developing colic-like symptoms after reserpine and xylazine has been reported. Until more is known about this potential interaction, use together of these two agents together should be avoided.

The manufacturers warn against using xylazine in conjunction with other tranquilizers.
Doses

Dogs

a) 1.1 mg/kg IV, 1.1 - 2.2 mg/kg IM or SC (Package Insert; Rompun® - Miles)
b) 0.6 mg/kg IV, IM as a sedative (Morgan 1988)
c) To treat a hypoglycemic crises (with IV dextrose): 1.1 mg/kg IM (Schall 1985)
d) 0.5 - 1.0 mg/kg IV or 1 - 2 mg/kg IM (Davis 1985b)
e) As an analgesic: 0.1 - 1 mg/kg IV, IM or SC. For post-operative anxiety: 0.1 - 0.5 mg/kg IV, IM or SC (Carroll 1999)

Cats

a) 1.1 mg/kg IV, 1.1 - 2.2 mg/kg IM or SC (Package Insert; Rompun®-Miles)
b) As an emetic: 0.44 mg/kg IM (Morgan 1988), (Riviere 1985)
c) As an analgesic: 0.1 - 1 mg/kg IV, IM or SC. For post-operative anxiety: 0.1 - 0.5 mg/kg IV, IM or SC (Carroll 1999)
d) 0.55 mg/kg IM (Mandsager 1988)

Rabbits/Rodents/Pocket Pets:

a) Rabbits: For minimally invasive procedures lasting less than 30-45 minutes: 5 mg/kg once SC or IM in combination with ketamine (35 mg/kg). Mice/Rats: General anesthesia 13 mg/kg once IP in combination with ketamine (87 mg/kg). Hamsters/Guinea pigs: General anesthesia 8 - 10 mg/kg once IP in combination with ketamine (200 mg/kg for hamsters & 60 mg/kg for Guinea pigs) (Huerkamp 1995)

Ferrets

a) As a sedative/analgesic: Xylazine: 0.5 - 2 mg/kg IM or SC. Usually combined with atropine (0.05 mg/kg) or glycopyrrolate (0.01 mg/kg IM) or Butorphanol/Xylazine: Butorphanol 0.2 mg/kg + Xylazine 2 mg/kg IM (Finkler 1999)
b) Xylazine (2 mg/kg) plus butorphanol (0.2 mg/kg) IM;
Telazol (1.5 mg/kg) plus xylazine (1.5 mg/kg) IM; may reverse xylazine with yohimbine (0.05 mg/kg IM)
Telazol (1.5 mg/kg) plus xylazine (1.5 mg/kg) plus butorphanol (0.2 mg/kg) IM; may reverse xylazine with yohimbine (0.05 mg/kg IM) (Williams 2000)

Birds

a) As a sedative/analgesic: 1 - 4 mg/kg IM, provides sedation for ketamine anesthesia. Has been used at dosages of up to 10 mg/kg in small psittacines (Clyde and Paul-Murphy 2000)

Cattle

Caution: Cattle are extremely sensitive to xylazine’s effects; be certain of dose and dosage form. Pretreatment with atropine can decrease the bradycardia and hypersalivation seen.

a) 0.05 - 0.15 mg/kg IV; 0.10 - 0.33 mg/kg IM. If administering IM use an 18 or 20 gauge needle at least 1.5 inches long. Intravenous route may stress cardiovascular function. (Thurmon and Benson 1986)
b) 0.044 - 0.11 mg/kg IV; 0.22 mg/kg IM (Mandsager 1988)
Horses

Note: ARCI UCGFS Class 3 Drug

a) 1.1 mg/kg IV; 2.2 mg/kg IM. Allow animal to rest quietly until full effect is reached. (Package Insert; Rompun® - Miles)

b) Sedative/analgesic for colic: 0.2 - 0.5 mg/kg IV (will provide analgesia for 20-30 minutes); or 0.6 - 1 mg/kg IM (effects for 1-2 hours). Evaluate heart rate prior to therapy. (Moore 1999)

c) For sedation/analgesia: Xylazine 0.5 - 1 mg/kg IV or IM with or without butorphanol (0.02 - 0.03 mg/kg). (Taylor 1999)

d) Prior to guaifenesin/thiobarbiturate anesthesia: 0.55 mg/kg IV; Prior to ketamine induction: 1.1 mg/kg IV; In combination with opioid/tranquilizers (all IV doses):

1)xylazine 0.66 mg/kg; meperidine 1.1 mg/kg
2)xylazine 1.1 mg/kg; butorphanol 0.01 - 0.02 mg/kg
3)xylazine 0.6 mg/kg; acepromazine 0.02 mg/kg

Note: the manufacturers state that xylazine should not be used in conjunction with tranquilizers (Thurmon and Benson 1987)

e) For field anesthesia: Sedate with xylazine (1 mg/kg IV; 2 mg/kg IM) given 5-10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either 1). Redose xylazine: up to half the original dose, 2) Add butorphanol (0.02-0.04 mg/kg IV). Butorphanol can be given with the original xylazine if you suspect that the horse will be difficult to tranquilize (e.g., high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5-10 minutes. 3) Diazepam (0.03 mg/kg IV). Mix the diazepam with the ketamine. This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5-10 minutes. 4) Guaifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)

Sheep & Goats

Note: Use xylazine with extreme caution in these species.

a)0.05 - 0.1 mg/kg IV; 0.10 - 0.22 IM (Thurmon and Benson 1986)

b)0.044 - 0.11 mg/kg IV; 0.22 mg/kg IM (Mandsager 1988)

Exotics

a) An excellent list of suggested dosages can be found on page 359 of Veterinary Pharmacology and Therapeutics, 6th Ed., Booth, NH & McDonald, LE, Eds.; 1988; Iowa State University Press; Ames, Iowa

Monitoring Parameters
1) Level of anesthesia/analgesia; 2) Respiratory function; cardiovascular status (rate, rhythm, BP if possible); 3) Hydration status if polyuria present

Client Information
Xylazine should only be used by individuals familiar with its use.

Dosage Forms/Preparations/FDA Approval Status/Withholding Times

Veterinary-Approved Products

Rompun® (Bayer) Gemini® (Butler); AnaSed® (Lloyd); Sedazine® (Fort Dodge) (Rx); Approved for use (depending on strength) in dogs, cats, horses, deer, and elk.

While xylazine is not approved for use in cattle in the USA, at labeled doses in Canada it reportedly has been assigned withdrawal times of 3 days for meat and 48 hours for milk. FARAD has reportedly suggested a withdrawal of 7 days for meat and 72 hours for milk for extra-label use in the USA.