Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Atracurium Besylate Injection: 10 mg/mL in 5 mL single-use and 10 mL multi-use vials; *Tracrium*® (GlaxoWellcome); Atracurium Besylate (Bedford Labs); (Rx)

ATROPINE SULFATE

(*a*-troe-peen)

ANTICHOLINERGIC

Prescriber Highlights

- Prototype antimuscarinic agent used for a variety of indications (bradycardia, premed, antidote, etc.)
- Contraindicated in conditions where anticholinergic effects would be detrimental (*e.g.*, narrow angle glaucoma, tachycardias, ileus, urinary obstruction, etc.)
- Adverse effects are dose related & anticholinergic in nature: 1) dry secretions, 2) initial bradycardia, then tachycardia, 3) slow gut & urinary tract, 4) mydriasis/cycloplegia
- Drug interactions

Uses/Indications

The principal veterinary indications for systemic atropine include:

- Preanesthetic to prevent or reduce secretions of the respiratory tract
- Treat sinus bradycardia, sinoatrial arrest, and incomplete AV block
- Differentiate vagally-mediated bradycardia for other causes
- As an antidote for overdoses of cholinergic agents (*e.g.*, physostigmine, etc.)
- As an antidote for organophosphate, carbamate, muscarinic mushroom, blue-green algae intoxication
- Hypersialism
- Treatment of bronchoconstrictive disease

Pharmacology/Actions

Atropine, like other antimuscarinic agents, competitively inhibits acetylcholine or other cholinergic stimulants at postganglionic parasympathetic neuroeffector sites. High doses may block nicotinic receptors at the autonomic ganglia and at the neuromuscular junction. Pharmacologic effects are dose related. At low doses salivation, bronchial secretions, and sweating (not horses) are inhibited. At moderate systemic doses, atropine dilates and inhibits accommodation of the pupil, and increases heart rate. High doses will decrease GI and urinary tract motility. Very high doses will inhibit gastric secretion.

Pharmacokinetics

Atropine sulfate is well absorbed after oral administration, IM injection, inhalation, or endotracheal administration. After IV administration peak effects in heart rates occur within 3–4 minutes.

Atropine is well distributed throughout the body and crosses into the CNS, across the placenta, and can distribute into the milk in small quantities.

Atropine is metabolized in the liver and excreted into the urine. Approximately 30–50% of a dose is excreted unchanged into the urine. The plasma half-life in humans has been reported to be between 2–3 hours.

Contraindications/Precautions/Warnings

Atropine is contraindicated in patients with narrow-angle glaucoma, synechiae (adhesions) between the iris and lens, hypersensitivity to anticholinergic drugs, tachycardias secondary to thyrotoxicosis or cardiac insufficiency, myocardial ischemia, unstable cardiac status during acute hemorrhage, GI obstructive disease, paralytic ileus, severe ulcerative colitis, obstructive uropathy, and myasthenia gravis (unless used to reverse adverse muscarinic effects secondary to therapy). Atropine may aggravate some signs seen with amitraz toxicity, leading to hypertension and further inhibition of peristalsis.

Antimuscarinic agents should be used with extreme caution in patients with known or suspected GI infections. Atropine or other antimuscarinic agents can decrease GI motility and prolong retention of the causative agent(s) or toxin(s) resulting in prolonged clinical signs. Antimuscarinic agents must also be used with extreme caution in patients with autonomic neuropathy.

Antimuscarinic agents should be used with caution in patients with hepatic or renal disease, geriatric or pediatric patients, hyperthyroidism, hypertension, CHF, tachyarrhythmias, prostatic hypertrophy, or esophageal reflux. Systemic atropine should be used cautiously in horses as it may decrease gut motility and induce colic in susceptible animals. It may also reduce the arrhythmogenic doses of epinephrine. Use of atropine in cattle may result in inappetence and rumen stasis that may persist for several days.

When used in food animals at doses up to 0.2 mg/kg, FARAD recommends a 28 day meat and 6 day milk withdrawal time. (Haskell, Payne et al. 2005)

Adverse Effects

Adverse effects are basically extensions of the drug's pharmacologic effects and are generally dose related. At usual doses, effects tend to be mild in relatively healthy patients. The more severe effects listed tend to occur with high or toxic doses. GI effects can include dry mouth (xerostomia), dysphagia, constipation, vomiting, and thirst. GU effects may include urinary retention or hesitancy. CNS effects may include stimulation, drowsiness, ataxia, seizures, respiratory depression, etc. Ophthalmic effects include blurred vision, pupil dilation, cycloplegia, and photophobia. Cardiovascular effects include sinus tachycardia (at higher doses), bradycardia (initially or at very low doses), hypertension, hypotension, arrhythmias (ectopic complexes), and circulatory failure.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*) Atropine use in pregnancy may cause fetal tachycardia.

Overdosage/Acute Toxicity

For signs and symptoms of atropine toxicity see adverse effects above. If a recent oral ingestion, emptying of gut contents and administration of activated charcoal and saline cathartics may be warranted. Treat clinical signs supportively and symptomatically. Do not use phenothiazines as they may contribute to the anticholinergic effects. Fluid therapy and standard treatments for shock may be instituted.

The use of physostigmine is controversial and should probably be reserved for cases where the patient exhibits either extreme agitation and is at risk for injuring themselves or others, or for cases where supraventricular tachycardias and sinus tachycardias are severe or life threatening. The usual dose for physostigmine (human) is: 2 mg IV slowly (for average sized adult). If no response, may repeat every 20 minutes until reversal of toxic antimuscarinic effects or cholinergic effects takes place. The human pediatric dose is 0.02 mg/kg slow IV (repeat q10 minutes as above) and may be a reasonable choice for initial treatment of small animals. Physostigmine adverse effects (bronchoconstriction, bradycardia, seizures) may be treated with small doses of IV atropine.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving atropine and may be of significance in veterinary patients:

The following drugs may enhance the activity or toxicity of atropine and its derivatives:

- **AMANTADINE**
- **ANTICHOLINERGIC AGENTS** (**other**)
- **ANTICHOLINERGIC MUSCLE RELAXANTS**
- **ANTIHISTAMINES** (*e.g.,* **diphenhydramine**)
- **DISOPYRAMIDE**
- **MEPERIDINE**
- **PHENOTHIAZINES**
- **PROCAINAMIDE**
- **PRIMIDONE**
- **TRICYCLIC ANTIDEPRESSANTS** (*e.g.,* **amitriptyline, clomipramine**)
- **AMITRAZ:** Atropine may aggravate some signs seen with amitraz toxicity; leading to hypertension and further inhibition of peristalsis
- **ANTACIDS:** May decrease PO atropine absorption; give oral atropine at least 1 hour prior to oral antacids
- **CORTICOSTEROIDS** (**long-term use**): may increase intraocular pressure
- **DIGOXIN** (**slow-dissolving**): Atropine may increase serum digoxin levels; use regular digoxin tablets or oral liquid
- **KETOCONAZOLE:** Increased gastric pH may decrease GI absorption; administer oral atropine 2 hours after ketoconazole
- **METOCLOPRAMIDE:** Atropine and its derivatives may antagonize the actions of metoclopramide

Doses

- **DOGS:**

As a preanesthetic adjuvant:

a) 0.022–0.044 mg/kg IM or SC (Muir)

b) 0.074 mg/kg IV, IM or SC (Package Insert; *Atropine Injectable*, S.A.—Fort Dodge)

c) 0.02–0.04 mg/kg SC, IM or IV (Morgan 1988)

For adjunctive treatment of bradycardias, Incomplete AV block, etc.:

a) 0.022–0.044 mg/kg IM, SC, or IV as needed; or 0.04 mg/kg PO three to four times daily (Morgan 1988)

b) 0.02–0.04 mg/kg IV or IM (Russell and Rush 1995)

To differentiate vagally-mediated bradyarrhythmias from non-vagal bradyarrhythmias (Atropine Response Test):

RISHNIW PREFERENCE: 1) Record ECG at baseline; 2) Administer 0.04 mg/kg atropine IV; 3) Wait 15 minutes; 4) Record ECG for at least 2 minutes (use slow paper speed). If the response is incomplete, repeat steps 2–4. Persistent sinus tachycardia at >140 bpm is expected in most dogs with vagally-mediated bradycardia.

KITTLESON PREFERENCE: 1) Record ECG at baseline; 2) Administer 0.04 mg/kg atropine SQ; 3) Wait 30 minutes; 4) Record ECG for at least 2 minutes (use slow paper speed). Persistent sinus tachycardia at >140 bpm is expected in most dogs with vagally-mediated bradycardia. (Rishniw and Kittleson 2007)

For treatment of cholinergic toxicity:

a) 0.2–2 mg/kg; give ¼th of the dose IV and the remainder SC or IM (Morgan 1988)

b) 0.2–0.5 mg/kg; ¼ of the dose IV and the remainder IM or SC (Firth 2000)

For treatment of bronchoconstriction:

a) 0.02–0.04 mg/kg for a duration of effect of 1–1.5 hours (Papich 1986)

- **CATS:**

As a preanesthetic adjuvant:

a) 0.022–0.044 mg/kg IM or SC (Muir)

b) 0.074 mg/kg IV, IM or SC (Package Insert; *Atropine Injectable, S.A.*—Fort Dodge)

c) 0.02–0.04 mg/kg SC, IM or IV (Morgan 1988)

For treatment of bradycardias:

a) 0.022–0.044 mg/kg IM, SC, or IV as needed; or 0.04 mg/kg PO three to four times daily (Morgan 1988)

b) 0.02–0.04 mg/kg SC, IM or IV q4–6h (Miller 1985)

For treatment of cholinergic toxicity:

a) 0.2–2 mg/kg; give ¼th of the dose IV and the remainder SC or IM (Morgan 1988)

b) 0.2–0.5 mg/kg; ¼ of the dose IV and the remainder IM or SC (Post and Keller 2000)

- **FERRETS:**

a) As a premed: 0.05 mg/kg SC or IM (Williams 2000)

- **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: For prevention of bradycardia, and to decrease airway secretions: 0.04–2 mg/kg; re-dosed q10–15 minutes as needed to produce mydriasis.

b) To treat organophosphate toxicity: 10 mg/kg SC q20 minutes (Ivey and Morrisey 2000)

- **CATTLE:**

Note: When used in food animals at doses up to 0.2 mg/kg, FARAD recommends a 28 day meat and 6 day milk withdrawal time. (Haskell, Payne et al. 2005)

As a preanesthetic:

a) Because of a lack of extended efficacy and potential adverse reactions, atropine is not used routinely as a preoperative agent in ruminants. If it is desired for use, a dose of 0.06–0.12 mg/kg IM has been suggested. (Thurmon and Benson 1986)

For adjunctive treatment of bovine hypersensitivity disease:

a) 1 gram per cow once daily followed by 0.5 gram/cow in 2–3 days (method of administration not specified) (Manning and Scheidt 1986)

For treatment of cholinergic toxicity (organophosphates):
a) 0.5 mg/kg (average dose); give ¼th of the dose IV and the remainder SC or IM; may repeat q3–4h for 1–2 days (Bailey 1986)

■ **HORSES:** (**Note:** ARCI UCGFS Class 3 Drug)

For treatment of bradyarrhythmias due to increased parasympathetic tone:
a) 0.01–0.02 mg/kg IV (Mogg 1999)
b) 0.045 mg/kg parenterally (Hilwig 1987)

As a bronchodilator:
a) 5 mg IV for a 400–500 kg animal (Beech 1987)
b) 5–7 mg/kg IV for a 450 kg horse can serve as a rescue medication in cases with severe airway obstruction, but it has an abbreviated duration of action (0.5–2 hours) and adverse effects (ileus, CNS toxicity, tachycardia, increased mucus secretion, and impaired mucociliary clearance) limit its use to a single rescue dose. (Rush 2006b)

For organophosphate poisoning:
a) Approximately 1 mg/kg given to effect, IV (use mydriasis and absence of salivation as therapy endpoints), may repeat every 1.5–2 hours as required subcutaneously (Oehme 1987)
b) 0.22 mg/kg, ¼th of the dose administered IV and the remainder SC or IM (Package Insert; *Atropine Injectable, L.A.*— Fort Dodge)

■ **SWINE:**

The equine dose (above) may be used to initially treat organophosphate toxicity in swine.

As an adjunctive preanesthetic agent:
a) 0.04 mg/kg IM (Thurmon and Benson 1986)

■ **SHEEP, GOATS:**

As a preanesthetic:
a) Because of a lack of extended efficacy and potential adverse reactions, atropine is not used routinely as a preoperative agent in ruminants. If it is desired for use, a dose of 0.15–0.3 mg/kg IM has been suggested. (Thurmon and Benson 1986)

For treating organophosphate toxicity:
a) Use the dose for cattle (above).

■ **BIRDS:**

For organophosphate poisoning:
a) 0.1–0.2 mg/kg IM or SC as needed (Clubb 1986)
b) 0.2 mg/kg IM every 3–4 hours as needed; ¼th the initial dose is administered. Use with pralidoxime (not in raptors) at 10–20 mg/kg IM q8–12h as needed. Do not use pralidoxime in carbamate poisonings.

To assist in diagnosing organophosphate poisoning (with history, clinical signs, etc.) in birds presenting with bradycardia: May administer atropine at 0.02 mg/kg IV. If bradycardia does not reverse, may consider organophosphate toxicity. (LaBond 2006)

As a preanesthetic:
a) 0.04–0.1 mg/kg IM or SC once (Clubb 1986)

■ **REPTILES:**

For organophosphate toxicity in most species:
a) 0.1–0.2 mg/kg SC or IM as needed. (Gauvin 1993)

For ptyalism in tortoises:
a) 0.05 mg/kg (50 cg/kg) SC or IM once daily (Gauvin 1993)

Monitoring

Dependent on dose and indication:
- Heart rate and rhythm
- Thirst/appetite; urination/defecation capability
- Mouth/secretions dryness

Client Information

- Parenteral atropine administration is best performed by professional staff and where adequate cardiac monitoring is available.
- If animal is receiving atropine systemically, allow animal free access to water and encourage drinking if dry mouth is a problem.

Chemistry/Synonyms

The prototype tertiary amine antimuscarinic agent, atropine sulfate is derived from the naturally occurring atropine. It is a racemic mixture of d-hyoscyamine and l-hyoscyamine. The l- form of the drug is active, while the d- form has practically no antimuscarinic activity. Atropine sulfate occurs as colorless and odorless crystals, or white, crystalline powder. One gram of atropine sulfate is soluble in approximately 0.5 mL of water, 5 mL of alcohol, or 2.5 mL of glycerin. Aqueous solutions are practically neutral or only slightly acidic. Commercially available injections may have the pH adjusted to 3.0–6.5.

Atropine may also be known as dl-hyoscyamine. Atropine sulfate may also be known as: atrop. sulph., atropine sulphate, or atropini sulfas; many trade names are available.

Storage/Stability/Compatibility

Atropine sulfate tablets or soluble tablets should be stored in well-closed containers at room temperature (15-30°C). Atropine sulfate for injection should be stored at room temperature; avoid freezing.

Atropine sulfate for injection is reportedly **compatible** with the following agents: benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, cimetidine HCl (not with pentobarbital), dimenhydrinate, diphenhydramine HCl, dobutamine HCl, droperidol, fentanyl citrate, glycopyrrolate, hydromorphone HCl, hydroxyzine HCl (also with meperidine), meperidine HCl, morphine sulfate, nalbuphine HCl, pentazocine lactate, pentobarbital sodium (OK for 5 minutes, not 24 hours), perphenazine, prochlorperazine edisylate, promazine HCl, promethazine HCl (also with meperidine), and scopolamine HBr.

Atropine sulfate is reported physically **incompatible** with norepinephrine bitartrate, metaraminol bitartrate, methohexital sodium, and sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Atropine Sulfate for Injection: 0.54 mg/mL (1/120 grain); *Atroject*® (Vetus), *Atropine SA*® (Butler), generic, (various); (Rx)

Atropine Sulfate for Injection: 15 mg/mL (organophosphate treatment) 100 mL vial; *Atropine L.A.*® (Butler), (RXV); generic (various) (Rx)

Atropine is labeled for use in dogs, cats, horses, cattle, sheep, and swine in the USA. No withdrawal times are mandated when used in food animals in the USA, but FARAD recommends a 28 day meat and 6 day milk withdrawal time. (Haskell, Payne et al. 2005). In the UK, slaughter withdrawal for cattle, sheep, and pigs is 14 days when used as an antimuscarinic and 28 days when used as an antidote; milk withdrawal is 3 days when used as an antimuscarinic and 6 days when used as an antidote. For guidance with determining use associated withdrawal times, contact FARAD (see Phone Numbers & Websites in the appendix)

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Atropine Sulfate for Injection:

0.05 mg/mL in 5 mL syringes; Atropine Sulfate (Hospira); (Rx)

0.1 mg/mL in 5 and 10 mL syringes; Atropine Sulfate (Hospira); (Rx)

0.3 mg/mL in 1 mL and 30 mL vials; generic; (Rx)

0.4 mg/mL in 1 mL amps and 1, 20, and 30 mL vials; generic; (Rx)

0.5mg/mL in 1 and 30 mL vials & 5 mL syringes; generic; (Rx)

0.8 mg/mL in 0.5 and 1 mL amps and 0.5 mL syringes; generic; (Rx)

1 mg/mL in 1 mL amps and vials and 10 mL syringes; generic; (Rx)

0.5 mg, 1 mg & 2 mg pre-filled, auto-injectors; *AtroPen*® (Meridian Medical Technologies); (Rx)

Atropine Sulfate Tablets:

0.4 mg; *Sal-Tropine*® (Hope); (Rx)

See also the monograph for atropine sulfate for ophthalmic use in the appendix. Atropine sulfate ophthalmic drops have been used buccally to decrease excessive oral secretions in human patients.

AURANOFIN

(au-***rane***-oh-fin) Ridaura®

ORAL GOLD IMMUNOSUPPRESSIVE

Prescriber Highlights

- Orally administered gold; used for pemphigus & idiopathic polyarthritis in dogs or cats
- Can be quite toxic & expensive, intensive ongoing monitoring required; dosages must be compounded from 3 mg capsules
- Probably less toxic, but also less efficacy than injectable gold
- Considered contraindicated in SLE (exacerbates)
- Known teratogen & maternotoxic
- Renal, hepatic & GI toxicity possible; dose dependent immune-mediated thrombocytopenia, hemolytic anemia or leukopenias have been seen

Uses/Indications

Auranofin has been used to treat idiopathic polyarthritis and pemphigus foliaceous in dogs and cats. Several clinicians report that while auranofin may be less toxic, it also less efficacious than injectable gold (aurothioglucose).

Pharmacology/Actions

Auranofin is an orally available gold salt. Gold has antiinflammatory, antirheumatic, immunomodulating, and antimicrobial (*in vitro*) effects. The exact mechanisms for these actions are not well understood. Gold is taken up by macrophages where it inhibits phagocytosis and may inhibit lysosomal enzyme activity. Gold also inhibits the release of histamine, and the production of prostaglandins. While gold does have antimicrobial effects *in vitro*, it is not clinically useful for this purpose. Auranofin suppresses helper T-cells, without affecting suppressor T-cell populations.

Pharmacokinetics

Unlike other available gold salts, auranofin is absorbed when given by mouth (20–25% of the gold) primarily in the small and large intestines. In contrast to the other gold salts, auranofin is only moderately bound to plasma proteins (the others are highly bound). Auranofin crosses the placenta and is distributed into maternal milk. Tissues with the highest levels of gold are kidneys, spleen, lungs, adrenals and liver. Accumulation of gold does not appear to occur, unlike the parenteral gold salts. About 15% of an administered dose (60% of the absorbed dose) is excreted by the kidneys, the remainder in the feces.

Contraindications/Precautions/Warnings

Auranofin should only be administered to animals where other less expensive and toxic therapies are ineffective and the veterinarian and owner are aware of the potential pitfalls of auranofin therapy and are willing to accept the associated risks and expenses. Gold salts are contraindicated in SLE as they may exacerbate the signs associated with this disease.

Adverse Effects

A dose dependent immune-mediated thrombocytopenia, hemolytic anemia or leukopenias have been noted in dogs. Discontinuation of the drug and administration of steroids has been recommended. Auranofin has a higher incidence of dose dependent GI disturbances (particularly diarrhea) in dogs than with the injectable products. Discontinuation of the drug or a lowered dose will generally resolve the problem. Renal toxicity manifested by proteinuria is possible as is hepatotoxicity (increased liver enzymes). These effects are less likely than either the GI or hematologic effects. Dermatosis and corneal ulcers have also been associated with auranofin therapy.

Reproductive/Nursing Safety

Auranofin has been demonstrated to be teratogenic and maternotoxic in laboratory animals; it should not be used during pregnancy unless the owner accepts the potential risks of use. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Following auranofin administration, gold is excreted in the milk of rodents. Trace amounts appear in the serum and red blood cells of nursing offspring. As this may cause adverse effects in nursing offspring, switching to milk replacer is recommended if auranofin is to be continued in the dam. Because gold is slowly excreted, persistence in milk will occur even after the drug is discontinued.

Overdosage/Acute Toxicity

Very limited data is available. The minimum lethal oral dose in rats is 30 mg/kg. It is recommended that gut-emptying protocols be employed after an acute overdose when applicable. Chelating agents (*e.g.*, penicillamine, dimercaprol) for severe toxicities have been used, but are controversial. One human patient who took an overdose over 10 days developed various neurologic sequelae, but eventually (after 3 months) recovered completely after discontinuation of the drug and chelation therapy.