ATENOLOL

(a-*ten*-oh-lol) Tenormin®

BETA-ADRENERGIC BLOCKER

Prescriber Highlights

- Beta-blocker that is used primarily for hypertension & tachyarrhythmias in small animals
- Has minimal beta-2 activity at usual doses; comparatively safe to use in asthmatic patients
- Contraindicated in patients with bradycardic arrhythmias, or hypersensitivity to it
- Negative inotrope so must be used with caution in patients with CHF; use with caution in renal failure patients & those with sinus node dysfunction
- Higher dosages may mask clinical signs of hyperthyroidism or hypoglycemia; may cause hyper- or hypoglycemia—use with caution in brittle diabetics
- Primary adverse effects are lethargy, hypotension, or diarrhea
- If discontinuing, recommend withdrawing gradually

Uses/Indications

Atenolol may be useful in the treatment of supraventricular tachyarrhythmias, premature ventricular contractions (PVC's, VPC's), systemic hypertension and in treating cats with hypertrophic cardiomyopathy. Atenolol is relatively safe to use in animals with bronchospastic disease.

Pharmacology/Actions

Atenolol is a relatively specific $Beta_1$-blocker. At higher dosages, this specificity may be lost and $Beta_2$ blockade can occur. Atenolol does not possess any intrinsic sympathomimetic activity like pindolol nor does it possess membrane-stabilizing activity like pindolol or propranolol. Cardiovascular effects secondary to atenolol's negative inotropic and chronotropic actions include: decreased sinus heart rate, slowed AV conduction, diminished cardiac output at rest and during exercise, decreased myocardial oxygen demand, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia.

Pharmacokinetics

Only about 50–60% of an oral dose is absorbed in humans, but is absorbed rapidly. In cats, it is reported to have a bioavailability of approximately 90%. The drug has very low protein binding characteristics (5–15%) and is distributed well into most tissues. Atenolol has low lipid solubility and unlike propranolol, only small amounts of atenolol are distributed into the CNS. Atenolol crosses the placenta and levels in milk are higher than those found in plasma. Atenolol is minimally biotransformed in the liver; 40–50% is excreted unchanged in the urine and the bulk of the remainder is excreted in the feces unchanged (unabsorbed drug). Reported half-lives: dogs = 3.2 hours; cats = 3.7 hours; humans = 6–7 hours. Duration of beta blockade effect in cats persists for about 12 hours.

Contraindications/Precautions/Warnings

Atenolol is contraindicated in patients with overt heart failure, hypersensitivity to this class of agents, greater than first-degree heart block, or sinus bradycardia. Non-specific beta-blockers are generally contraindicated in patients with CHF unless secondary to a tachyarrhythmia responsive to beta-blocker therapy. They are also relatively contraindicated in patients with bronchospastic lung disease.

Atenolol should be used cautiously in patients with significant renal insufficiency or sinus node dysfunction.

Atenolol (at high dosages) can mask the clinical signs associated with hypoglycemia. It can also cause hypoglycemia or hyperglycemia and, therefore, should be used cautiously in labile diabetic patients.

Atenolol can mask the clinical signs associated with thyrotoxicosis, however, it may be used clinically to treat the clinical signs associated with this condition.

Adverse Effects

It is reported that adverse effects most commonly occur in geriatric animals or those that have acute decompensating heart disease. Adverse effects considered clinically relevant include: bradycardia, inappetance, lethargy and depression, impaired AV conduction, CHF or worsening of heart failure, hypotension, hypoglycemia, and bronchoconstriction (less so with $Beta_1$ specific drugs like atenolol). Syncope and diarrhea have also been reported in canine patients with beta-blockers. Lethargy and hypotension may be noted within 1 hour of administration.

Exacerbation of symptoms has been reported following abrupt cessation of beta-blockers in humans. It is recommended to withdraw therapy gradually in patients who have been receiving the drug chronically.

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.*)

Overdosage/Acute Toxicity

There were 208 exposures to atenolol reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 145 were dogs with 11 showing clinical signs, 62 cases were cats with 4 showing clinical signs and the remaining reported case was a bird that showed no clinical signs. Common findings in dogs recorded in decreasing frequency included bradycardia, lethargy and arrhythmia. Common findings in cats recorded in decreasing frequency included: coma, lethargy, protrusion of the third eyelid, subdued, and vomiting.

Humans have apparently survived dosages of up to 5 grams. The most predominant clinical signs expected would be extensions of the drug's pharmacologic effects: hypotension, bradycardia, bronchospasm, cardiac failure and hypoglycemia.

If overdose is secondary to a recent oral ingestion, emptying the gut and charcoal administration may be considered. Monitor: ECG, blood glucose, potassium and, if possible, blood pressure. Treatment of the cardiovascular effects is symptomatic. Use fluids and pressor agents to treat hypotension. Bradycardia may be treated with atropine. If atropine fails, isoproterenol given cautiously has been recommended. Use of a transvenous pacemaker may be necessary. Cardiac failure can be treated with a digitalis glycoside, diuretics and oxygen. Glucagon (5–10 mg IV; human dose) may increase heart rate and blood pressure and reduce the cardiodepressant effects of atenolol.

Drug Interactions

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

- **ANESTHETICS** (**myocardial depressant**): Additive myocardial depression may occur with the concurrent use of atenolol and myocardial depressant anesthetic agents
- **CALCIUM-CHANNEL BLOCKERS** (*e.g.,* **diltiazem, verapamil, amlodipine**): Concurrent use of beta-blockers with calcium channel blockers (or other negative inotropics) should be done with caution, particularly in patients with preexisting cardiomyopathy or CHF
- **CLONIDINE:** Atenolol may exacerbate rebound hypertension after stopping clonidine therapy
- **FUROSEMIDE, HYDRALAZINE OR OTHER HYPOTENSIVE PRODUCING DRUGS:** May increase the hypotensive effects of atenolol
- **PHENOTHIAZINES:** With atenolol may exhibit enhanced hypotensive effects
- **RESERPINE:** Potential for additive effects (hypotension, bradycardia)
- **SYMPATHOMIMETICS** (**metaproterenol, terbutaline, beta-effects of epinephrine, phenylpropanolamine,** etc.): May have their actions blocked by atenolol and they may, in turn, reduce the efficacy of atenolol

Doses

- **DOGS:**

  For indications where beta-blockade may be indicated (cardiac arrhythmias, obstructive heart disease, hypertension, myocardial infarction, etc.):

  a) 0.2–1 mg/kg PO q12–24h (Ware 2000)
  b) 0.25–1 mg/kg PO q12–24h (Hogan 2004)
  c) 6.25–25 mg (total dose) PO q12h (Muir and Bonagura 1994); (Fuentes 1999)
  d) For moderate to severe sub-valvular aortic stenosis (SAS): 0.5–1 mg/kg PO twice a day (Meurs 2006c)
  e) To attempt to decrease syncopal episodes associated with pulmonic stenosis: 0.25–1 mg/kg PO twice a day (Meurs 2006c)

  For treatment of hypertension:

  a) 0.25–1 mg/kg PO q12h (Stepian 2006b)
  b) For hypertension: 0.5 mg/kg initially PO q12–24h; may combine with vasodilators and/or diuretics (Brown and Henik 2000)
  c) 0.25–1 mg/kg PO q12–24h (Snyder and Cooke 2005)

- **CATS:**

  For treatment of hypertension:

  a) 2 mg/kg once daily; hyperthyroid cats being started on methimazole are treated usually for 2 weeks with atenolol. It is important to closely monitor geriatric cats as renal disease may be a concurrent problem with hyperthyroidism or hypertension. (Littman 1992)
  b) 6.25–12.5 mg per cat per day. Starting dose should be low and titrate to effect. Do not start treatment immediately prior to anesthesia or surgery without a suitable period of dosage titration. (Mooney and Thoday 2000)
  c) 0.5 mg/kg initially PO q12–24h; may combine with vasodilators and/or diuretics (Brown and Henik 2000)
  d) 2 mg/kg PO q12–24h (Snyder and Cooke 2005)
  e) 6.25–12.5 mg (total dose) PO q12–24h. Treatment of choice for hyperthyroid, hypertensive cats. Beta-blockers are rarely sufficient alone to treat hypertension due to other causes. (Waddell 2005)
  f) 3 mg/kg PO q12h (or 6.25–12.5 mg total dose) PO q12h (Stepian 2006b)

  For indications where beta blockade may be indicated (cardiac arrhythmias, obstructive heart disease, hypertension, myocardial infarction, etc.):

  a) 6.25–12.5 mg (total dose) PO q12–24h (Ware and Keene 2000); (Fox 2000)

- **FERRETS:**

  For hypertrophic cardiomyopathy:

  a) 6.25 mg (total dose) PO once daily (Williams 2000)
  b) 3.13–6.25 mg (total dose) PO once daily (Johnson-Delaney 2005c)

Monitoring

- Cardiac function, pulse rate, ECG if necessary, BP if indicated
- Toxicity (see Adverse Effects/Overdosage)

Client Information

- To be effective, the animal must receive all doses as prescribed. Notify veterinarian if animal becomes lethargic or becomes exercise intolerant; develops shortness of breath or cough; or develops a change in behavior or attitude. Do not stop therapy without first conferring with veterinarian.

Chemistry/Synonyms

A beta$_1$-adrenergic blocking agent, atenolol occurs as a white, crystalline powder. At 37°C, 26.5 mg are soluble in 1 mL of water. The pH of the commercially available injection is adjusted to 5.5–6.5.

Atenolol may also be known as atenololum, or ICI-66082; many trade names are available.

Storage/Stability/Compatibility

Tablets should be stored at room temperature and protected from heat, light and moisture. The injection solution should be stored at room temperature and protected from light.

Atenolol injection is reported to be physically **compatible** with morphine sulfate injection and meperidine HCl for at least 4 hours. Dextrose injections, sodium chloride injections and combinations of the two are recommended for use as diluents when given parenterally.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

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

HUMAN-LABELED PRODUCTS:

Atenolol Tablets: 25, 50, & 100 mg; *Tenormin*® (AstraZeneca); generic; (Rx)

Atenolol Injection: 5 mg/mL in 10 mL amps; *Tenormin*®(AstraZeneca); (Rx)

Also available in an oral fixed dose combination product with chlorthalidone.

ATIPAMEZOLE HCL

(at-i-*pam*-a-zole) Antisedan®

ALPHA-2 ADRENERGIC ANTAGONIST

Prescriber Highlights

- Alpha$_2$ adrenergic antagonist; antagonizes agonists such as medetomidine or xylazine
- No safety data on use in pregnant or lactating animals
- May reverse effects rapidly, including analgesia; animals should be observed & protected from self-harm or causing harm to others
- Adverse Effects may include vomiting, diarrhea, hypersalivation, tremors, or excitation

Uses/Indications

Atipamezole is labeled for use as a reversal agent for medetomidine and dexmedetomidine. It potentially could be useful for reversal of other alpha$_2$-adrenergic agonists as well (*e.g.*, amitraz, xylazine, clonidine, tizanidine, brimonidine).

Pharmacology/Actions

Atipamezole competitively inhibits alpha$_2$-adrenergic receptors, thereby acting as a reversal agent for alpha$_2$-adrenergic agonists (*e.g.*, medetomidine). Net pharmacologic effects are to reduce sedation, decrease blood pressure, increase heart and respiratory rates, and reduce the analgesic effects of alpha$_2$-adrenergic agonists.

Pharmacokinetics

After IM administration in the dog, peak plasma levels occur in about 10 minutes. Atipamezole is apparently metabolized in the liver to compounds that are eliminated in the urine. The drug has an average plasma elimination half-life of about 2–3 hours.

Contraindications/Precautions/Warnings

While the manufacturer lists no absolute contraindications to the use of atipamezole, the drug is not recommended in pregnant or lactating animals due to the lack of data establishing safety. Caution should be used in administration of anesthetic agents to elderly or debilitated animals.

When used as a reversal agent (antidote) for alpha$_2$-agonist toxicity, atipamezole's effects may subside before non-toxic levels of the offending agent are reached; repeat dosing may be necessary.

Adverse Effects

Potential adverse effects include occasional vomiting, diarrhea, hypersalivation, tremors, and brief excitation or apprehensiveness.

Because reversal can occur rapidly, care should be exercised as animals emerging from sedation and analgesia may exhibit apprehensive or aggressive behaviors. After reversal, animals should be protected from falling. Additional analgesia (*e.g.*, butorphanol) should be considered, particularly after painful procedures.

Reproductive/Nursing Safety

The manufacturer states that the drug is not recommended in pregnant or lactating animals, or in animals intended for breeding due to lack of data establishing safety in these animals. No other data was noted.

Overdosage/Acute Toxicity

Dogs receiving up to 10X the listed dosage apparently tolerated the drug without major effects. When overdosed, dose related effects seen included panting, excitement, trembling, vomiting, soft or liquid feces, vasodilatation of sclera and some muscle injury at the IM injection site. Specific overdose therapy should generally not be necessary.

Drug Interactions

The manufacturer states that information on the use of atipamezole with other drugs is lacking, therefore, caution should be taken when using with other drugs (other than medetomidine). The following drug interactions have either been reported or are theoretical in humans or animals receiving atipamezole and may be of significance in veterinary patients:

- **ALPHA1-ADRENERGIC BLOCKERS** (*e.g.*, **prazosin**): Atipamezole is a relatively specific alpha-2 blocker it can also partially block alpha1 receptors and reduce the effects of prazosin
- **ALPHA2-ADRENERGICS AGONISTS** (*e.g.*, **detomidine, clonidine, brimonidine, xylazine, amitraz,** etc.): Atipamezole can reduce the effects (toxic or therapeutic) of these agents

Doses

- **DOGS:**

  For reversal of medetomidine:

  a) Give IM an equal volume of *Antisedan*® and *Domitor*® is administered (mL per mL). The actual concentration of *Antisedan*® will be 5X that of *Domitor*®, as *Antisedan*® is 5 mg/mL versus *Domitor*®'s 1 mg/mL. (Package Insert; *Antisedan*®—Pfizer)

  b) As above, but may give IV as well as IM. If it has been at least 45 minutes since medetomidine was given, may give atipamezole at half the volume of medetomidine if administered IV. If after 10–15 minutes an IM dose of atipamezole has not seemed to reverse the effects of medetomidine, an additional dose of atipamezole at ½ the volume of the medetomidine dose may be given. (McGrath and Ko 1997)

  For treatment of amitraz toxicity:

  a) 50 mcg/kg IM (Hugnet, Buronrosse et al. 1996)

- **CATS:**

  For reversal of medetomidine as part of a medetomidine/ butorphanol or buprenorphine/ketamine/carprofen or meloxicam anesthesia/analgesia injectable combination:

  a) Use an equal volume IM of atipamezole as medetomidine was used in the combination. (Ko 2005)

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

  a) Rabbits: For medetomidine reversal: 1 mcg/kg SC, IV or IP. Will reverse analgesia as well. (Ivey and Morrisey 2000)

  b) Mice, Rats, Gerbils, Hamsters, Guinea pigs: To reverse xylazine or medetomidine: 0.1–1 mg/kg IM, IP, IV or SC (Adamcak and Otten 2000)

- **RUMINANTS:**

  a) For reversal of alpha$_2$-adrenergic agonists in bovine, new world camelids, ovine and caprine species: 0.02–0.1 mg/kg IV to effect (Haskell 2005b)

- **BIRDS:**

  a) As a reversal agent for alpha$_2$-adrenergic agonists (*e.g.*, xylazine, detomidine, etc.): 0.5 mg/kg IM (Clyde and Paul-Murphy 2000)