DIGOXIN

(di-*jox*-in) Lanoxin®, Cardoxin®

CARDIAC GLYCOSIDE

Prescriber Highlights

- Oral & parenteral cardiac glycoside used for CHF & SVT's in many species; usually with other agents
- Contraindications: V-fib, digitalis intoxication; many veterinarians feel that digoxin is relatively contraindicated in cats with hypertrophic cardiomyopathy
- Extreme Caution: Patients with glomerulonephritis & heart failure or with idiopathic hypertrophic subaortic stenosis (IHSS)
- Caution: Severe pulmonary disease, hypoxia, acute myocarditis, myxedema, or acute MI, frequent VPC's V-tach, chronic constrictive pericarditis or incomplete AV block
- Adverse Effects usually associated with high or toxic blood levels: Cardiac effects may include almost every type of cardiac arrhythmia described with a resultant worsening of heart failure clinical signs. Extracardiac: mild GI upset, anorexia, weight loss & diarrhea
- Drug Interactions
- Monitoring of blood levels highly suggested

Uses/Indications

The veterinary indications for digoxin include treatment of congestive heart failure, atrial fibrillation or flutter, and supraventricular tachycardias.

Digoxin therapy is controversial for treating heart failure. Today, many cardiologists no longer feel that digoxin is first line therapy for heart failure in dogs and cats and with the availability of pimobendan this trend is expected to continue. Many state that digoxin can have beneficial effects in certain patients when used with diuretics and, possibly, ACE inhibitors, but digoxin alone is rarely, if ever, used for heart failure.

Pharmacology/Actions

The pharmacology of the digitalis glycosides have been extensively studied, but a thorough discussion is beyond the scope of this reference. Digitalis glycosides cause the following effects in patients with a failing heart: increased myocardial contractility (inotropism) with increased cardiac output; increased diuresis with reduction of edema secondary to a decrease in sympathetic tone; reduction in heart size, heart rate, blood volume, and pulmonary and venous pressures; and (usually) no net change in myocardial oxygen demand.

The digitalis glycosides have several electrocardiac effects, including: decreased conduction velocity through the AV node, and prolonged effective refractory period (ERP). They may increase the PR interval, decrease the QT interval and cause ST segment depression.

The exact mechanism of action of these agents has not been fully described, but their ability to increase the availability of Ca^{++} to myocardial fibers and to inhibit Na^{+}-K^{+}-ATPase with resultant increased intracellular Na^{+} and reduced K^{+} probably explains their actions.

For additional information, it is suggested to refer to a pharmacology text.

Pharmacokinetics

Absorption following oral administration occurs in the small intestine and is variable dependent upon the oral dosage form used (see Dosage Forms below). Food may delay, but not alter, the extent of absorption in most species studied. Food reportedly decreases the amount absorbed by 50% in cats after tablet administration. Peak serum levels generally occur within 45–60 minutes after oral elixir and about 90 minutes after oral tablet administration. In patients receiving an initial oral dose of digoxin, peak effects may occur in 6–8 hours after the dose.

The drug is distributed widely throughout the body with highest levels found in kidneys, heart, intestine, stomach, liver and skeletal muscle. Lowest concentrations are found in the brain and plasma. Digoxin does not significantly enter ascitic fluid, so dosage adjustments may be required in animals with ascites. At therapeutic levels, approximately 20–30% of the drug is bound to plasma proteins. Because only small amounts are found in fat, obese patients may receive dosages too high if dosing is based on total body weight versus lean body weight.

Digoxin is metabolized slightly, but the primary method of elimination is renal excretion both by glomerular filtration and tubular secretion. As a result, dosage adjustments must be made in patients with significant renal disease. Values reported for the elimination half-life of digoxin in dogs and cats have been highly variable, with values reported from 14.4–56 hours for dogs; 30–173 hours for cats. Elimination half-lives reported in other species include: Sheep≈7.15 hours; Horses≈16.9–23.2 hours; and Cattle≈7.8 hours.

Contraindications/Precautions/Warnings

Many cardiologists feel that digoxin is relatively contraindicated in cats with hypertrophic cardiomyopathy as it may increase myocardial oxygen demand and lead to dynamic outflow obstruction.

Digoxin is actively transported by the p-glycoprotein pump and certain breeds susceptible to MDR1-allele mutation (Collies, Australian Shepherds, Shelties, Long-haired Whippet) are at higher risk for toxicity, particularly CNS effects.

Digitalis cardioglycosides are contraindicated in patients with ventricular fibrillation or in digitalis intoxication. They should be used with extreme caution in patients with glomerulonephritis and heart failure or with idiopathic hypertrophic subaortic stenosis (IHSS). They should be used with caution in patients with severe pulmonary disease, hypoxia, acute myocarditis, myxedema, or acute myocardial infarction, frequent ventricular premature contractions, ventricular tachycardias, chronic constrictive pericarditis or incomplete AV block. They may be used in patients with stable, complete AV block or severe bradycardia with heart failure if the block was not caused by the cardiac glycoside.

When used to treat atrial fibrillation or flutter prior to administration with an antiarrhythmic agent that has anticholinergic activity (*e.g.*, quinidine, procainamide, disopyramide), digitalis glycosides will reduce, but not eliminate, the increased ventricular rates that may be produced by those agents. Since digitalis glycosides may cause increased vagal tone, they should be used with caution in patients with increased carotid sinus sensitivity.

Elective cardioversion of patients with atrial fibrillation should be postponed until digitalis glycosides have been withheld for 1–2 days, and should not be attempted in patients with signs of digitalis toxicity.

Principally eliminated by the kidneys, digoxin should be used with caution and serum levels monitored in patients with renal disease. Animals that are hypernatremic, hypokalemic, hypercalcemic, hyper- or hypothyroid may require smaller dosages; monitor carefully.

Adverse Effects

Adverse effects of digoxin are usually associated with high or toxic serum levels and are categorized into cardiac and extracardiac clinical signs. There are species differences with regard to the sensitivity to digoxin's toxic effects also. Cats are relatively sensitive to digoxin while dogs tend to be more tolerant of high serum levels.

Cardiac effects may be seen before other extra-cardiac clinical signs and may include almost every type of cardiac arrhythmia described with a resultant worsening of heart failure clinical signs. More common arrhythmias or ECG changes observed include: complete or incomplete heart block, bigeminy, ST segment changes, paroxysmal ventricular or atrial tachycardias with block, and multifocal premature ventricular contractions. Because these effects can also be caused by worsening heart disease, it may be difficult to determine if they are a result of the disease process or digitalis intoxication. If in doubt, monitor serum levels or stop digoxin therapy temporarily.

Extracardiac clinical signs most commonly seen in veterinary medicine include mild GI upset, anorexia, weight loss, and diarrhea. Vomiting has been associated with IV injections and should not cause anxiety or alarm. Ocular and neurologic effects are routinely seen in humans, but are not prevalent in animals or are not detected.

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: ***A*** (*Probably safe. Although specific studies may not have proved the safety of all drugs in dogs and cats, there are no reports of adverse effects in laboratory animals or women.*)

Studies have shown that digoxin concentrations in mother's serum and milk are similar; however, it is unlikely to have any pharmacological effect in nursing offspring.

Overdosage/Acute Toxicity

Clinical signs of chronic toxicity are discussed above. In dogs the acute toxic dose after IV administration has been reported to be 0.177 mg/kg.

Treatment of chronic digoxin toxicity is dictated by the severity of the clinical signs associated with it. Many patients will do well after temporarily stopping the drug and reevaluating the dosage regimen.

If an acute ingestion has recently occurred and no present cardiotoxic or neurologic signs (coma, seizures, etc.) have manifested, emptying the stomach may be indicated followed with activated charcoal administration. Because digoxin can be slowly absorbed and there is some enterohepatic recirculation of the drug, repeated charcoal administration may be beneficial even if the ingestion occurred well before treatment. Anion-exchange resins such as colestipol or cholestyramine have been suggested to reduce the absorption and enterohepatic circulation of digoxin, but are not readily available in most veterinary practices.

Dependent on the type of cardiotoxicity, supportive and symptomatic therapy should be implemented. Serum electrolyte concentrations, drug level if available on a "stat" basis, arterial blood gases if available, and continuous ECG monitoring should be instituted. Acid-base, hypoxia, and fluid and electrolyte imbalances should be corrected. The use of potassium in normokalemic patients is very controversial and should only be attempted with constant monitoring and clinical expertise.

The use of specific antiarrhythmic agents in treating life-threatening digitalis-induced arrhythmias may be necessary. Lidocaine and phenytoin are most commonly employed for these arrhythmias. Atropine may be used to treat sinus bradycardia, SA arrest, or 2nd or 3rd degree AV block.

Digoxin immune Fab is a promising treatment for digoxin or digitoxin life-threatening toxicity. It is produced from specific digoxin antibodies from sheep and will bind directly to the drug, inactivating it. It is very expensive however and veterinary experience with it is extremely limited.

Drug Interactions

There are many potential drug interactions associated with digoxin and the following list is not necessarily all inclusive. Because of the narrow therapeutic index associated with the drug, consider enhanced monitoring when these drugs (are those in the same class) are added to patients stabilized on digoxin.

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

The following drugs may **reduce digoxin serum levels:**

- **AMINOSALICYLIC ACID**
- **ANTACIDS**
- **CHOLESTYRAMINE**
- **CIMETIDINE**
- **METOCLOPRAMIDE**
- **NEOMYCIN** (**oral**)
- **St JOHN'S WORT**
- **SULFASALAZINE**

The following agents may **increase serum levels, decrease the elimination rate, or enhance the toxic effects** of digoxin:

- **AMIODARONE**
- **ANTICHOLINERGICS**
- **CAPTOPRIL** (or other **ACEIs**)
- **DIAZEPAM**
- **DILTIAZEM** (data conflicts)
- **ERYTHROMYCIN**
- **FUROSEMIDE**
- **KETOCONAZOLE/ITRACONAZOLE**
- **OMEPRAZOLE** (or other **PPIs**)
- **QUINIDINE**
- **RESERPINE**
- **SUCCINYLCHOLINE**
- **TETRACYCLINE**
- **VERAPAMIL**
- **BETA-BLOCKERS**: Can have additive negative effects on AV conduction, complete heart block possible
- **CALCIUM-CHANNEL BLOCKERS** (**diltiazem**, etc.): Can have additive negative effects on AV conduction
- **PENICILLAMINE**: May decrease serum levels of digoxin independent of route of digoxin dosing.
- **POTASSIUM/ELECTROLYTE BALANCE, DRUGS AFFECTING** (*e.g.*, **diuretics, amphotericin B, glucocorticoids, laxatives, sodium polystyrene sulfonate, glucagon, high dose IV dextrose, dextrose/insulin infusions, furosemide, thiazides**): May predispose the patient to digitalis toxicity
- **SPIRONOLACTONE**: May enhance or decrease the toxic effects of digoxin
- **THYROID SUPPLEMENTS**: Patients on digoxin that receive thyroid replacement therapy may need their digoxin dosage adjusted

Laboratory Considerations

- No specific laboratory test concerns
- Digoxin can cause prolonged PR interval and ST segment depression, and false-positive changes on EKG ST-T in human patients during exercise testing

Doses

- **DOGS:**
  a) Because of the variability in pharmacokinetics in individual animals, administration to any animal should be considered a pharmacological "experiment":
  Initially, in dogs weighing less than 18 kg (40 lbs.) give 0.0044–0.011 mg/kg PO q12h. In dogs weighing more than 18 kg (40 lbs), initial dose is 0.25 mg/M2 PO q12h. Monitor for signs of toxicity and efficacy and measure serum concentration 3–5 days later (draw sample 6–8 hours after last dose) to see if therapeutic (0.5–2 ng/mL). Readjust dosage accordingly. (Kittleson 2000)
  b) Initial dose: 0.005–0.01 mg/kg q12h (up to a maximum of 0.375 mg, or rarely, 0.5 mg/day). Use lean body weight to determine dosage. Measure serum digoxin level 5–10 days later. Draw level 8–10 hours after dosing. Therapeutic level: 1–2 ng/mL. If level is less than 0.8 ng/mL, increase dose up to 30% and repeat serum level monitoring as above. If toxicity is suspected, stop therapy for at least 1–2 days and then resume at a reduced dose (by 50%). (Ware and Keene 2000)
  c) For adjunctive treatment of atrial fibrillation: 0.003–0.005 mg/kg PO q12h (Hogan 2004)
  d) If pimobendan is not available or too expensive, especially if refractory heart failure exists or atrial fibrillation is observed: Start with a low dose (0.005 mg/kg PO twice a day) and round down if needed. (Meurs 2006b)
- **CATS:**
  For dilated cardiomyopathy or advanced atrioventricular valve insufficiency (**Note:** digoxin is generally contraindicated for feline hypertrophic cardiomyopathy):
  a) Initial dose: 0.007 mg/kg PO every other day. Use lean body weight to determine dosage. Measure serum digoxin level 10+ days later. Draw level 8–10 hours after dosing. Therapeutic level: 1–2 ng/mL. If level is less than 0.8 ng/mL, increase dose up to 30% and repeat serum level monitoring as above. If toxicity is suspected, stop therapy for at least 1–2 days and then resume at a reduced dose (by 50%). (Ware and Keene 2000)
  b) Tablets: 0.005–0.008 mg/kg/day PO divided twice daily
  Alternatively: For cats weighing: 2–3 kg = ¼ of a 0.125 mg tablet every other day; 4–5 kg = ¼ of a 0.125 mg tablet every day; 6 kg or > or = ¼ of a 0.125 mg tablet twice daily (Kittleson 1985a)
  c) Oral maintenance 0.007–0.015 mg/kg once daily to every other day. Rapid IV: 0.005 mg/kg lean body weight divided between three doses (1/2 the dose initially, then 60 minutes later another ¼ of the dose, 60 minutes later the remainder (if necessary) or to effect. Stop if marked bradycardia, diminished AV conduction, other digoxin related arrhythmias or clinical signs of toxicity are present. Begin oral therapy as soon as the last IV dose is completed. (Miller 1985)
- **FERRETS:**
  For adjunctive therapy for heart failure:
  a) For dilated cardiomyopathy: 0.01 mg/kg PO once daily initially (use oral liquid). May increase to twice daily if necessary. Monitor as per dogs and cats. (Hoeffer 2000)
  b) 0.005–0.01 mg/kg PO once to twice daily using the elixir; for maintenance; monitor blood levels if possible (Williams 2000)
  c) Treatment follows the same principles of other small animal medicine: Dilated cardiomyopathy long-term maintenance with furosemide (2 mg/kg q12h), enalapril (0.5 mg/kg q48h) and digoxin (0.01 mg/kg q24h). Monitor potassium if using diuretics longer than a few days. (Johnson-Delaney 2005c)
- **RABBITS/RODENTS/SMALL MAMMALS:**
  a) Hamsters: For dilated cardiomyopathy: 0.05–0.1 mg/kg PO q12h (Adamcak and Otten 2000)
- **CATTLE:**
  a) 0.25 mg/100 lbs body weight (not destroyed in rumen), titrate dose to normalize atrial rate; not excreted in milk (McConnell and Hughey 1987)
- **HORSES:** (**Note:** ARCI UCGFS Class 4 Drug)
  a) Loading dose: 11 mcg/kg IV given slowly or in divided doses, *or* 44 mcg/kg PO;
  Maintenance Dose: 2.2 mcg/kg IV every 12h or 11 mcg/kg PO every 12 hours. Maintain plasma concentrations between 0.5–2 ng/mL. (Mogg 1999)
- **BIRDS:**
  a) Because of its very small therapeutic margin, it may be best to use digoxin to stabilize patients in an emergency rather than for long-term therapy; initial doses are 0.02–0.5 mg/kg q12h for 2–3 days, then decreased to 0.01 mg/kg q12–24h. Consider switching to an ACE inhibitor. (Johnson-Delaney 2005a)

Monitoring

- Serum levels: Because of the significant interpatient pharmacokinetic variation seen with this drug, and its narrow therapeutic index, it is strongly recommended to monitor serum levels to help guide therapy. Unless the patient received an initial loading dose, at least 6 days should pass after beginning therapy to monitor serum levels to allow levels to approach steady-state. Suggested therapeutic serum levels in the dog are 0.9–3 ng/mL (some believe that levels above 2.5 ng/mL are "poisonous") and 0.9–2 ng/mL in cat (Neff-Davis 1985). For other species, values from 0.5–2 ng/mL can be used as guidelines. Levels at the higher end of the suggested range may be necessary to treat some atrial arrhythmias, but may also result in higher incidences of adverse effects. Usually a trough level (just before next dose or at least 8 hours after last dose) is recommended, but drawing a sample anytime is acceptable
- Appetite/weight
- Cardiac rate, ECG changes
- Serum electrolytes
- Clinical efficacy for CHF (improved perfusion, decreased edema, increased venous (or arterial) O2 levels).

Client Information

- Contact veterinarian if animal demonstrates changes in behavior, vomits, has diarrhea, shows lack of appetite, clinical signs of colic (horses), or becomes lethargic or depressed.

Chemistry/Synonyms

A cardiac glycoside, digoxin occurs as bitter tasting, clear to white crystals or as white, crystalline powder. It is practically insoluble in water, slightly soluble in diluted alcohol, and very slightly soluble in 40% propylene glycol solution. Above 235°C, it melts with decomposition.

Digoxin may also be known as: digoxinum or digoxosidum; many trade names are available. Occasionally, digoxin is described as digitalis.

Storage/Stability/Compatibility

The commercial injection consists of a 40% propylene glycol, 10% alcohol solution having a pH of 6.6–7.4.

Digoxin tablets, capsules, elixir and injection should be stored at room temperature (15–30°C) and protected from light.

At pH's from 5–8, digoxin is stable, but in solutions with a pH of less than 3, it is hydrolyzed.

The injectable product is **compatible** with most commercially available IV solutions, including lactated Ringer's, D_5W, and normal saline. To prevent the possibility of precipitation occurring, one manufacturer (GlaxoWellcome) recommends that the injection be diluted by a volume at least 4 times; with either sterile water, D_5W, or normal saline. Digoxin injection has been demonstrated to be **compatible** with bretylium tosylate, cimetidine HCl, lidocaine HCl, and verapamil HCl.

Digoxin is **incompatible** with dobutamine HCl, acids, and alkalies. The manufacturer does not recommend mixing digoxin injection with other medications. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

There are bioavailability differences between dosage forms and in tablets produced by different manufacturers. It is recommended that tablets be used from a manufacturer that the clinician has confidence in and that brands not be routinely interchanged. Should a change in dosage forms be desired, the following bioavailability differences can be used as guidelines in altering the dose: Intravenous = 100%, IM ≈ 80%, Oral tablets ≈ 60%, Oral elixir ≈ 75%, Oral capsules ≈ 90–100%. The bioavailability of digoxin in veterinary species has only been studied in a limited manner. One study in dogs yielded similar values as those above for oral tablets and elixir, but in horses only about 20% of an intragastric dose was bioavailable.

VETERINARY-LABELED PRODUCTS:

The veterinary-labeled products are no longer available commercially in the USA.

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Digoxin for Injection: 0.1 mg/ mL in 1 mL amps (pediatric) and 0.25 mg/mL in 2 mL amps, and 1 and 2 mL *Tubex* or *Carpuject*; *Lanoxin*® (Glaxo Wellcome); (Rx); generic; (Rx)

Digoxin Tablets: 0.125 mg, and 0.25 mg; *Lanoxin*® (Glaxo Wellcome); *Digitek*® (Bertek Pharm); generic; (Rx)

Digoxin Capsules: 0.05 mg, 0.1 mg & 0.2 mg; *Lanoxicaps*® (Cardinal Health); (Rx)

Digoxin Elixir Pediatric: 0.05 mg/mL in 60 mL dropper bottle, and UD 2.5 and 5 mL; generic; (Rx)

DIHYDROTACHYSTEROL
DHT

(dye-*hye*-droe-*tak*-ee-ster-ole) DHT®, Hytakerol®

VITAMIN D ANALOG

Prescriber Highlights

- Commercial dosage forms reportedly discontinued; may be available from compounding pharmacies
- Vitamin D analog for hypocalcemia secondary to hypoparathyroidism or renal disease
- Raises calcium faster than ergocalciferol & effects dissipate more rapidly after the drug is stopped
- Contraindications: Hypercalcemia, vitamin D toxicity, malabsorption syndrome, or abnormal sensitivity to the effects of vitamin D. Extreme caution: hyperphosphatemia, renal dysfunction (when receiving the drug for non-renal indications)
- Adverse Effects: Hypercalcemia (may present as polydipsia, polyuria & anorexia), nephrocalcinosis, & hyperphosphatemia
- Some animals are resistant to therapy
- Monitoring serum calcium mandatory

Uses/Indications

DHT is used in small animals to treat hypocalcemia secondary to hypoparathyroidism or severe renal disease.

Pharmacology/Actions

DHT is hydroxylated in the liver to 25-hydroxy-dihydrotachysterol that is the active form of the drug and is an analog of 1,25-dihydroxyvitamin D. Vitamin D is considered a hormone and, in conjunction with parathormone (PTH) and calcitonin, regulates calcium homeostasis in the body. Active analogues (or metabolites) of vitamin D enhance calcium absorption from the GI tract, promote reabsorption of calcium by the renal tubules, and increase the rate of accretion and resorption of minerals in bone.

Pharmacokinetics

If fat absorption is normal, vitamin D analogs are readily absorbed from the GI tract (small intestine). There are anecdotal reports of dogs and cats not responding to the oral tablets or capsule forms of the drug, but responding to the oral liquid dosage forms. Bile is required for adequate absorption and patients with steatorrhea, liver or biliary disease will have diminished absorption. DHT is hydroxylated in the liver to 25-hydroxy-dihydrotachysterol that is the active form of the drug. Unlike some other forms of vitamin D, DHT does not require parathormone activation in the kidneys. The time required for maximal therapeutic effect is usually seen within the first week of treatment. Unlike some other forms of vitamin D, DHT offloads relatively rapidly (1–3 weeks).

Contraindications/Precautions/Warnings

DHT is contraindicated in patients with hypercalcemia, vitamin D toxicity, malabsorption syndrome, or abnormal sensitivity to the effects of vitamin D. It should be used with extreme caution in patients with hyperphosphatemia (many clinicians believe hyperphosphatemia or a combined calcium/phosphorous product of >70 mg/dl is a contraindication to its use), or in patients with renal dysfunction (when receiving the drug for non-renal indications).