DIAZEPAM

(dye-*az*-e-pam) Valium®, Diastat®

BENZODIAZEPINE

Prescriber Highlights

- Benzodiazepine used for a variety of indications (anxiolytic, muscle relaxant, hypnotic, appetite stimulant, & anticonvulsant) in several species
- Contraindications: 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 & ataxia most prevalent. DOGS: CNS excitement; CATS: Hepatic failure or behavior changes; HORSES: Muscle fasciculations
- Inject IV slowly
- May be teratogenic
- Drug interactions
- Controlled substance (C-IV)

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.

Pharmacology/Actions

The subcortical levels (primarily limbic, thalamic, and hypothalamic), of the CNS are depressed by diazepam and other benzodiazepines 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.

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. In dogs, rectally administered diazepam has an average bioavailability of 50%, but significant interpatient variation occurs. When administered intranasally to dogs, bioavailability is about 80%.

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:

	DOGS	CATS	HORSES	HUMANS
Diazepam	2.5 – 3.2 hrs	5.5 hrs	7–22 hrs	20–50 hrs
Nordiazepam	3 hrs	21.3 hrs		30–200 hrs

Contraindications/Precautions/Warnings

Inject intravenously slowly. This is particularly true when using a small vein for access or in small animals; diazepam may cause significant thrombophlebitis. Rapid 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.

Adverse Effects

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 (not dose dependent) for several days. Clinical signs (anorexia, lethargy, increased ALT/AST, hyperbilirubinemia) have been reported to occur 5–11 days after beginning oral therapy. Cats that receive diazepam should have baseline liver function tests. These should be repeated and the drug discontinued if emesis, lethargy, inappetence or ataxia develops.

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.

Reproductive/Nursing Safety

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. In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug*

in pregnant women may be acceptable despite its potential risks.) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Benzodiazepines and their metabolites are distributed into milk and may cause CNS effects in nursing neonates.

Overdosage/Acute Toxicity

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) is generally not recommended. Flumazenil may be considered for adjunctive treatment of overdoses of benzodiazepines.

Drug Interactions

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

- **AMITRIPTYLINE:** Diazepam may increase levels
- **ANTACIDS:** May decrease oral diazepam absorption
- **ANTIFUNGALS, AZOLE** (**itraconazole, ketoconazole**, etc.): May increase diazepam levels
- **CIMETIDINE:** May decrease metabolism of benzodiazepines
- **CNS DEPRESSANT DRUGS** (**barbiturates, narcotics, anesthetics,** etc.): If diazepam administered with other CNS depressant agents additive effects may occur
- **DEXAMETHASONE:** May decrease diazepam levels
- **DIGOXIN:** Diazepam may increase digoxin levels
- **ERYTHROMYCIN:** May decrease the metabolism of benzodiazepines
- **MINERAL OIL:** May decrease oral diazepam absorption
- **PHENOBARBITAL:** May decrease diazepam concentrations
- **PHENYTOIN:** May decrease diazepam concentrations
- **QUINIDINE:** May increase diazepam levels
- **RIFAMPIN:** May induce hepatic microsomal enzymes and decrease the pharmacologic effects of benzodiazepines

Laboratory Considerations

- 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, but should not be given within 10 minutes of the prior dose. Owners should stay with dog for one hour after administration. (Podell 2000), (Podell 2006b)

  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 status epilepticus: 0.5–1 mg/kg IV, 1–2 mg/kg per rectum; may need to be re-dosed, a long-acting anticonvulsant (*e.g.*, phenobarbital) must be administered to gain complete control. (Knipe 2006b)

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

  e) For methylxanthine (*e.g.*, theophylline) induced seizures: 0.5–2 mg/kg IV (if unsuccessful, use phenobarbital at 6 mg/kg IV q6–12h) (Hooser and Beasley 1986)

  f) For salicylate toxicity induced seizures: 2.5–20 mg (total dose) IV or PO (Handagama 1986)

  g) 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 three to four times daily (Morgan 1988)

  For Scotty cramp:

  a) 0.5–2 mg/kg IV to effect or PO three times daily (Morgan 1988)

  As a preanesthetic:

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

  For irritable colon syndrome:

  a) 0.15 mg/kg PO three times daily (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 three times a day; 0.5 mg/kg IV (Chew, DiBartola, and Fenner 1986)

  c) 0.2 mg/kg PO q8h or 2–10 mg (total dose) PO q8h (Bartges 2003a)

  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 as needed (Morgan 1988)

  For adjunctive treatment of metronidazole toxicity (CNS):

  a) Doses of diazepam averaged 0.43 mg/kg in the study and were given as an IV bolus once, and then PO q8h for 3 days. (Evans, Levesque et al. 2002)

- **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 in 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 adjunctive treatment of feline psychogenic alopecia and dermatitis:

  a) 1–2 mg PO twice daily (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. (Shell 2000)

b) For oral maintenance therapy of seizures: As a second choice drug (after phenobarb): 0.5–1 mg/kg PO q12h (Quesnel 2000)

c) 0.5–1 mg/kg/day PO dose is divided every 8–12 hours. Drug has a wide margin of safety and dosages as high as 2 mg/kg may be required in some cats. (Munana 2004c)

d) For salicylate toxicity induced seizures: 2.5–5 mg IV or PO (Handagama 1986)

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)

c) 2.5–5 mg (total dose) PO q8h or as needed, or 0.5 mg/kg IV (Bartges 2003a)

■ **FERRETS:**

For premedication/sedation:

a) 1–2 mg/kg IM; may be given with ketamine (10–20 mg/kg) (Morrisey and Carpenter 2004)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: Pre-anesthetic: 2–10 mg/kg IM; 1–5 mg/kg IM or IV. Give IV to effect for seizures. (Ivey and Morrisey 2000)

b) Rabbits: As a tranquilizer (to increase relaxation of lightly anesthetized animals and permit ET intubation): 1 mg/kg IV as needed (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:**

a) Sedative in calves: 0.4 mg/kg IV (Booth 1988a)

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

c) Treatment of CNS hyperactivity and seizures: 0.5 – 1.5 mg/kg IM or IV (Bailey 1986b)

■ **HORSES:** (**Note:** ARCI UCGFS Class 2 Drug)

For field anesthesia:

a) 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)

For seizures:

a) Foals: 0.05–0.4 mg/kg IV; repeat in 30 minutes if necessary

b) 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 are 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)

c) For sedation prior to pentobarbital anesthesia: 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 (with analgesics):

a) 0.5–2 mg/kg IV or IM (Clyde and Paul-Murphy 2000)

Monitoring

■ Horses should be observed carefully after receiving this drug.

■ Cats receiving diazepam should have baseline liver function tests. Repeat and discontinue 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

■ Cats: If patient develops lack of appetite, vomits, or yellowish whites of eyes contact veterinarian immediately

Chemistry/Synonyms

A benzodiazepine, diazepam is a white to yellow, practically odorless crystalline powder with a melting point between 131°–135°C and pK_a of 3.4. Diazepam is tasteless initially, but develops a bitter after-taste. 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.

Diazepam may also be known as: diazepamum, LA-III, NSC-77518, or Ro-5-2807; many trade names are available.

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 D_5W. Differing results have occurred with different manufacturer's products. Do not administer if a precipitate forms and does not clear.

While mixing diazepam with ketamine in a single syringe is not recommended, it is often done in veterinary medicine with apparent success; however, it should be used immediately after mixing and excess medication should not be saved. Do not use if a visible precipitate forms.

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:

Diazepam Tablets: 2 mg, 5 mg, & 10 mg; *Valium*® (Roche); generic; (Rx, C-IV)

Diazepam Oral Solution: 1 mg/mL in 30 mL with dropper, 500 mL, and 5 mg and 10 mg patient cups; generic, *Diazepam Intensol*® (Roxane); (Rx, C-IV)

Diazepam Injection: 5 mg/mL in 2 mL *Carpuject* cartridges; generic; (Rx, C-IV)

Diazepam Rectal Gel: 2.5 mg, 10 mg, 20 mg; *Diastat*® (Xcel); (Rx, C-IV)

DIAZOXIDE, ORAL

(di-az-*ok*-side) Proglycem®, Hyperstat IV®

DIRECT VASODILATOR/HYPERGLYCEMIC

Prescriber Highlights

- **Orally administered drug used to treat insulinomas in small animals**
- **Contraindications/Cautions: Functional hypoglycemia or hypoglycemia secondary to insulin overdosage (diabetics); hypersensitive to thiazide diuretics; CHF or renal disease**
- **Adverse Effects: Most likely are anorexia, vomiting &/or diarrhea (may be reduced by giving with food). Less likely: tachycardia, hematologic abnormalities, diabetes mellitus, cataracts, & sodium & water retention. Adverse effects are more likely in dogs with hepatic disease.**
- **Availability & expense issues**

Uses/Indications

Oral diazoxide is used in canine and ferret medicine for the treatment of hypoglycemia secondary to hyperinsulin secretion (*e.g.*, insulinoma). Insulinomas are apparently very rare in the cat; there is little experience with this drug in that species.

In human medicine, intravenous diazoxide is sometimes used for treating severe hypertension.

Pharmacology/Actions

Although related structurally to the thiazide diuretics, diazoxide does not possess any appreciable diuretic activity. By directly causing a vasodilatory effect on the smooth muscle in peripheral arterioles, diazoxide reduces peripheral resistance and blood pressure. To treat malignant hypertension, intravenous diazoxide is generally required for maximal response.

Diazoxide exhibits hyperglycemic activity by directly inhibiting pancreatic insulin secretion. This action may be a result of the drug's capability to decrease the intracellular release of ionized calcium, thereby preventing the release of insulin from the insulin granules. Diazoxide does not apparently affect the synthesis of insulin, nor does it possess any antineoplastic activity. Diazoxide also enhances hyperglycemia by stimulating the beta-adrenergic system thereby stimulating epinephrine release and inhibiting the uptake of glucose by cells.

Pharmacokinetics

The serum half-life of diazoxide has been reported to be about 5 hours in the dog; other pharmacokinetic parameters in the dog appear to be unavailable. In humans, serum diazoxide (at 10 mg/kg PO) levels peaked at about 12 hours after dosing with capsules. It is unknown what blood levels are required to obtain hyperglycemic effects. Highest concentrations of diazoxide are found in the kidneys with high levels also found in the liver and adrenal glands. Approximately 90% of the drug is bound to plasma proteins and it crosses the placenta and into the CNS. It is not known if diazoxide is distributed into milk. Diazoxide is partially metabolized in the liver and is excreted as both metabolites and unchanged drug by the kidneys. Serum half-life of the drug is prolonged in patients with renal impairment.

Contraindications/Precautions/Warnings

Diazoxide should not be used in patients with functional hypoglycemia or for treating hypoglycemia secondary to insulin overdosage in diabetic patients. Unless the potential advantages outweigh the risks, do not use in patients hypersensitive to thiazide diuretics.

Because diazoxide can cause sodium and water retention, use cautiously in patients with congestive heart failure or renal disease.

Adverse Effects

When used to treat insulinomas in dogs, the most commonly seen adverse reactions include hypersalivation, anorexia, vomiting and/or diarrhea; these effects may be lessened by administering the drug with food. Other effects that may be seen include: tachycardia, hematologic abnormalities (agranulocytosis, aplastic anemia, thrombocytopenia), diabetes mellitus, cataracts (secondary to hyperglycemia?), and sodium and water retention.

Administering the drug with meals or temporarily reducing the dose may alleviate the gastrointestinal side effects. Adverse effects may be more readily noted in dogs with concurrent hepatic disease.

Adverse effects reported with diazoxide use in ferrets include: inappetence, vomiting, diarrhea, and bone marrow suppression.

The drug is reportedly very bitter.