PHENOBARBITAL SODIUM
PHENOBARBITAL

(fee-noe-*bar*-bi-tal)

BARBITURATE

Prescriber Highlights

- Barbiturate used primarily as an antiseizure medication; also used as a sedative agent
- Contraindications: Known hypersensitivity, severe liver disease, nephritis, or severe respiratory depression (large doses)
- Caution: Hypovolemia, anemia, borderline hypoadrenal function, or cardiac or respiratory disease; use with caution in cats (sensitive to respiratory depression)
- Adverse Effects: DOGS: Anxiety/agitation or lethargy (when initiating treatment); profound depression, (even at low doses) is 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.
- Adverse Effects: CATS: Ataxia, lethargy, polyphagia/weight gain & polydipsia/polyuria. Rare: Immune-mediated reactions & 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

Uses/Indications

Although some believe that bromide salts are now the treatment of first choice for treating epilepsy in dogs (especially young dogs and those with liver disease), many still choose phenobarbital for dogs because of its favorable pharmacokinetic profile, relative safety, efficacy, low cost, and ability to treat epilepsy at sub-hypnotic doses. Phenobarbital is still widely considered the drug of first choice for treating epilepsy in cats. It is also occasionally used as an oral sedative agent in both 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 may also useful in controlling excessive feline vocalization while riding in automobiles.

In cattle, the microsomal enzyme stimulating properties of phenobarbital has 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.

Pharmacology/Actions

While barbiturates are generally considered 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 patient age, physical condition, or concurrent use of other drugs. The barbiturates depress the sensory cortex, lessen motor activity, and produce sedation at low dosages. 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 doses four times lower than those will cause cardiac arrest. These drugs must be used very cautiously in cats; they are particularly sensitive to the respiratory depressant effects of barbiturates.

The barbiturates cause reduced tone and motility of the intestinal musculature, probably secondary to its central depressant action. Administration of barbiturates reduces the sensitivity of the motor endplate 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.

Pharmacokinetics

The pharmacokinetics of phenobarbital have been thoroughly studied in humans and 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 along 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. An elimination half-life of 34–43 hours has 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. Alkalinizing the urine and/or substantially increasing urine flow will increase excretion rates. Anuric or oliguric patients may accumulate unmetabolized drug; dosage adjustments may need to be made.

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

Contraindications/Precautions/Warnings

Use cautiously in patients that 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

Dogs may exhibit increased clinical signs 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; 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 are reversible if detected early. Increases in liver enzymes are well described for phenobarbital in dogs and are not necessarily indicative of liver dysfunction, but if serum ALT or ALP are greater than 4–5 times the upper limit of normal, or if any elevation of AST and GGT are noted, it should raise concern. Phenobarbital should generally be discontinued if any increases in serum bilirubin, total serum bile acids or hypoalbumenemia are seen. Frank hepatic failure is uncommon and is usually associated with higher serum levels (>30–40 mcg/mL).

Phenobarbital may rarely cause superficial necrolytic dermatitis (SND) in dogs associated with changes in hepatocytes (severe parenchymal collapse with glycogen-laden hepatocytes and moderate fibrosis sharply demarcated by nodules of normal hepatic parenchyma) distinct from that seen with phenobarbital hepatotoxicity.

Cats may develop ataxia, persistent sedation and lethargy, polyphagia/weight gain, and polydipsia/polyuria. Rarely, immune-mediated reactions and bone marrow hypoplasia (thrombocytopenia, neutropenia) may be seen. Cats, unlike dogs, apparently do not have the issues of increased liver enzymes. Very high dosages (10–40 mg/kg/day) have caused coagulopathies in cats.

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

Reproductive/Nursing Safety

Phenobarbital has been associated with rare congenital defects and bleeding problems in newborns, but may be safer than other anticonvulsants. 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 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.*)

Exercise caution when administering to a nursing mother since small amounts are excreted in maternal milk. Drowsiness in nursing offspring has been reported.

Overdosage/Acute Toxicity

There were 346 exposures to phenobarbital reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 304 were dogs with 54 showing clinical signs and the remaining 42 reported cases were cats with 10 showing clinical signs. Common findings in dogs recorded in decreasing frequency included ataxia, sedation, lethargy, coma and recumbency. Common findings in cats recorded in decreasing frequency included vomiting, ataxia, mydriasis, sedation, blindness and central nervous system depression.

Treatment of a phenobarbital overdose consists of removal of ingested product from the gut, if appropriate, and giving 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 drug interactions have either been reported or are theoretical in humans or animals receiving phenobarbital and may be of significance in veterinary patients:

- **ACETAMINOPHEN**: Increased risk for hepatotoxicity, particularly when large or chronic doses of barbiturates are given
- **MONAMINE OXIDASE (MAO) INHIBITORS** (*e.g.*, **amitraz**, possibly **selegiline**): May prolong phenobarbital effects
- **PHENYTOIN**: Barbiturates may affect the metabolism of phenytoin, and phenytoin may alter barbiturate levels; monitoring of blood levels may be indicated
- **RIFAMPIN**: May induce enzymes that increase the metabolism of barbiturates

The following drugs may increase the effects of phenobarbital:

- **ANTIHISTAMINES**
- **CHLORAMPHENICOL**
- **OPIATES**
- **PHENOTHIAZINES**
- **VALPROIC ACID**

Phenobarbital (particularly after chronic therapy) may decrease the effect of the following drugs/drug classes by lowering their serum concentrations:

- **ANTICOAGULANTS, ORAL (WARFARIN)**
- **BETA-BLOCKERS**
- **CHLORAMPHENICOL**
- **CLONAZEPAM**
- **CORTICOSTEROIDS**
- **CYCLOSPORINE**
- **DOXORUBICIN**
- **DOXYCYCLINE** (may persist for weeks after barbiturate discontinued)

- **ESTROGENS**
- **GRISEOFULVIN**
- **METHADONE**
- **METRONIDAZOLE**
- **QUINIDINE**
- **PAROXETINE**
- **PHENOTHIAZINES**
- **PROGESTINS**
- **THEOPHYLLINE**
- **TRICYCLIC ANTIDEPRESSANTS**
- **VERAPAMIL**

Laboratory Considerations

- 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 a false positive low dose **dexamethasone suppression test**, by increasing the clearance of dexamethasone. Phenobarbital apparently has no effect either on ACTH stimulation tests or on the hormonal equilibrium of the adrenal axis.

Doses

- **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)

  d) Loading dose of 16–20 mg/kg once IV; maintenance dose of 2–5 mg/kg PO q12h. (Knipe 2006a)

  e) Begin at 3.5 mg/kg PO twice daily. Monitor at 2 to 4 weeks and 3 months later to detect induction. If response is insufficient, increase dose sufficiently to increase trough level by 3 to 5 mcg/mL increments, rechecking at 2 to 4 weeks after each dose increase. Monitor at 3 to 12 month intervals once steady–state is achieved. As concentrations approach 30 mcg/mL, begin monitoring hepatic function test (bile acids, albumin, BUN, chol). As concentrations approach 35 mcg/mL, consider adding an additional drug. Avoid any other drug metabolized by the liver. Consider hepatoprotectant drugs if liver dysfunction is of concern. (Axlund 2004b)

  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 twice daily (Walton 1986)

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

  c) For adjunctive treatment 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)

  c) Loading dose of 16–20 mg/kg once IV; maintenance dose of 1–5 mg/kg PO q12h. (Knipe 2006a)

  d) Starting dose is 1–2 mg/kg (usually 3.25–15 mg/cat) PO q12h. Measure trough serum levels 2–3 weeks after initiating therapy and after each dosage change. In the cat, therapeutic levels are likely 50–100 mcmol/L (lower than those in dogs). If seizure control is good, but levels are subtherapeutic, dose does not need to be increased. Measure phenobarbital levels, CBC and serum chemistries every 6 months. (Cochrane 2007)

  Sedation; for controlling excessive feline vocalization for situational distress (*e.g.*, riding in automobiles):

  a) 2–3 mg/kg PO as needed (Overall 2000)

- **FERRETS:**

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

  b) Loading dose of 16–20 mg/kg once IV; maintenance dose of 1–2 mg/kg PO q8–12h. (Knipe 2006a)

- **CATTLE:**

  For enzyme induction in organochlorine toxicity:

  a) 5 grams PO for 3–4 weeks, off 3–4 weeks, then 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) Adult horses: Loading dose of 16–20 mg/kg once IV; maintenance dose of 1–5 mg/kg PO twice daily.

  Foals: Loading dose of 16–20 mg/kg once IV; maintenance dose of 100–500 mg (total dose) PO twice daily. (Knipe 2006a)

  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

- Anticonvulsant (or sedative) efficacy
- Adverse effects (CNS related, PU/PD, weight gain)
- Serum phenobarbital levels if lack of efficacy or adverse reactions

noted. Some recommend that all dogs have their phenobarbital level monitored once a year and cats monitored every 6 months. Although there is some disagreement among clinicians, therapeutic serum levels in dogs (15–45 mcg/mL; 65-194 mcmol/L) are thought to be similar to those in humans. Therapeutic levels in cats may be closer to 12–30 mcg/mL (50–129 mcmol/L). Animals on bromides and phenobarbital may require lower serum levels for seizure control. If phenobarbital was not "loaded", wait at least 5–6 half-lives (approximately 12–14 days in dogs and 9–10 days in cats) before measuring serum concentrations; time of sampling does not appear to be significant

- If used chronically, routine CBC's, liver enzymes (especially ALT and AST), and bilirubin at least every 6 months.

Client Information

- For successful epilepsy treatment compliance with prescribed therapy must be stressed. 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 clinical signs of anemia and/or liver disease) or seizure control is unacceptable.

Chemistry/Synonyms

Phenobarbital, a barbiturate, occurs as white, glistening, odorless, small crystals or a white, crystalline powder with a melting point of 174°–178°C and a pK_a of 7.41. One gram is soluble in approximately 1000 mL of water; 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.

SI units (mcmol/L) are multiplied by 0.232 to convert phenobarbital levels to conventional units (mcg/mL).

Phenobarbital may also be known as fenobarbital, phenemalum, phenobarbitalum, phenobarbitone, phenylethylbarbituric acid, or phenylethylmalonylurea, *Luminal Sodium*® and *Solfoton*®.

Storage/Stability/Compatibility

Phenobarbital tablets should be stored in tight, light-resistant containers at room temperature (15–30°C); protect from moisture. Phenobarbital elixir should be stored in tight containers at 20–20°C.

Phenobarbital sodium injection should be stored at room temperature (15–30°C).

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, atropine sulfate (stable for at least 15 minutes, but not 24 hours), calcium chloride and gluconate, cephapirin 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), meperidine HCl, morphine sulfate, nalbuphine HCl, norepinephrine bitartrate, oxytetracycline HCl, pentazocine lactate, procaine HCl, prochlorperazine edisylate, promazine HCl, promethazine HCl, and streptomycin sulfate. 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

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:

Phenobarbital Tablets: 15 mg, 16 mg (tablets and capsules), 30 mg, 60 mg, 90 mg, & 100 mg; *Solfoton*® (ECR Pharm); generic; (Rx, C-IV)

Phenobarbital Elixir: 15 mg/5mL in pt and UD 5 mL, 10 mL and 20 mL; 20 mg/5mL in pt, gal, UD 5 mL and 7.5 mL; generic; (Rx, C-IV)

Phenobarbital Sodium Injection: 30 mg/mL, 60 mg/mL, 65 mg/mL, & 130 mg/mL in 1 mL *Tubex, Carpujects* and vials; *Luminal Sodium*® (Hospira); generic; (Rx; C-IV)

PHENOXYBENZAMINE HCL

(fen-ox-ee-*ben*-za-meen) Dibenzyline®

ALPHA-ADRENERGIC BLOCKER

Prescriber Highlights

- **Alpha-adrenergic blocker used in small animals: detrusor areflexia, pheochromocytoma (hypertension); horses: laminitis or diarrhea**
- **Contraindications: When hypotension would be deleterious; possibly glaucoma or diabetes mellitus, horses with clinical signs of colic. Caution: CHF or other heart disease, renal damage, or cerebral/coronary arteriosclerosis**
- **Adverse Effects: Hypotension, hypertension (rebound), miosis, increased intraocular pressure, tachycardia, inhibition of ejaculation, nasal congestion, weakness/dizziness, & GI effects (*e.g.*, nausea, vomiting). Constipation may occur in horses.**
- **May need to be obtained from compounding pharmacy**
- **Drug Interactions**

Uses/Indications

Phenoxybenzamine is used in small animals primarily for its effect in reducing internal urethral sphincter tone in dogs and cats when urethral sphincter hypertonus is present. It can also be used to treat the hypertension associated with pheochromocytoma prior to surgery or as adjunctive therapy in endotoxicosis.

In horses, phenoxybenzamine has been used for preventing or treating laminitis in its early stages and to treat secretory diarrheas.