

# Treatment of Phenobarbital Overdose by Hemodialysis in a Cat with Suspected Porto-Systemic Shunt

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## ABSTRACT

The management of phenobarbital overdose using hemodialysis in a cat with suspected portosystemic shunt is described. An 8 year old British blue intact male cat was referred due to convulsions and stupor. The cat had a lifelong history of abnormal behavior and convulsions every approximately 6 months. The cat was tentatively diagnosed with portosystemic shunt based on high serum ammonia concentrations and abdominal ultrasound. The cat was hospitalized for further diagnosis and treatment, and was accidentally overdosed with phenobarbital at 25 mg/kg IM. Hemodialysis was performed in an attempt to enhance clearance of the drug. Phenobarbital levels decreased gradually during the treatment, however, there was no improvement in the neurological status of the cat and the owners elected euthanasia. To the best of the author's knowledge, this is the first report demonstrating the utility of hemodialysis in the management of phenobarbital overdose in small animals.

**Keywords:** Feline; Toxicosis; Barbiturate; Convulsion.

## INTRODUCTION

Phenobarbital is a commonly used anticonvulsant in companion animals. Similar to other barbiturates, Phenobarbital binds to the  $\beta$ -subunit of the  $\gamma$ -aminobutyric acid A (GABA-A) receptor, prolonging the opening of chloride ion channel, thereby potentiating the neuro-inhibitory effect of GABA (1). Phenobarbital is a long-acting barbiturate, with a narrow therapeutic index (10-30  $\mu$ g/ml) and wide inter-individual metabolic rate variability (2). Its narrow therapeutic index implies that its therapeutic concentration is close to the toxic concentration. Hence, its serum concentration should be monitored. Phenobarbital overdose might induce central nervous system (CNS) depression, respiratory failure and cardiovascular instability. Consequently, phenobarbital overdose is a medical emergency. The common emergent

treatment of phenobarbital overdose in small animals includes decontamination (if exposure was oral and recent), and alkaline diuresis, as well as symptomatic, supportive measures (2).

This report describes a phenobarbital overdose in a cat with suspected porto-systemic shunt (PSS) that was managed, among other measures using hemodialysis.

## CASE REPORT

An 8-year old British Shorthair intact male cat was referred to the hospital due to convulsions and stupor. It was a strictly indoor cat, and exposure to environmental poisons was ruled out. It was described by its owners as always being quiet, and had repeated episodes of star gazing and nodding. Seizure episodes manifested as "wall climbing" had occurred once to

twice every six months. Each such episode had lasted several minutes up to one hour, with a post-ictal period lasting several hours.

On one occasion, prior to presentation, the cat had ceased eating and drinking, and was later found convulsing in a puddle of urine, and then appeared unresponsive. At the referring clinic, it was treated with diazepam per rectum and 100 mL of saline subcutaneously. At presentation to the hospital, the cat was in a state of stupor. It had a heart rate of 220 beats/minute, rectal temperature of 38.2°C and respiratory rate of 40 breaths/min. It showed drooling, absence of the menace reflex, slow pupillary light response, and a normal palpebral reflex. Blood glucose level (Accu-Chek® sensor glucometer Roche, Mannheim, Germany) was within reference interval (RI) (99 mg/dL; RI 63-118). The systolic/diastolic arterial blood pressures were 142/100 mmHg, respectively. Laboratory abnormalities at presentation (Advia 120, Siemens Medical Solutions Diagnostics, Erfurt, Germany, Cobas-Integra 400 Plus, Roche, Mannheim, Germany) included anemia (hematocrit 24%; RI 24-45), microcytosis (mean corpuscular volume [MCV] 36  $\mu$ L; RI, 39-55), hypoalbuminemia (albumin 2.0 g/dL; RI 2.2-4.6), hypocholesterolemia (cholesterol 67mg/dL; RI 89-258), low urea concentration (18 mg/dL; RI 35-70), hyperbilirubinemia (0.41 mg/dl; RI, 0.0-0.2) and hyperammonemia (plasma ammonia 322  $\mu$ mol/L; RI <68).

Abdominal ultrasonography showed microhepatica, with diffuse liver hyperechogenicity and mild heterogeneity. The right portal branch was demonstrated, but not the left one. Both kidneys were slightly enlarged, with a medullary rim sign. The tentative diagnosis was of portosystemic shunt (PSS), however, no additional diagnostic tests were carried out to confirm the diagnosis.

The cat was hospitalized for further diagnostic measures and treatment. Therapy during hospitalization included IV fluids (Saline, Teva medical, Ashdod, Israel, 4.2 mL/kg/hr), ampicillin (Penibrin, Sandoz GmbH, Kundl Austria, 25 mg/kg, IV, q8h), metronidazole (Metronidazole, Braun, Melsungen, Germany, 7.5 mg/kg, IV, q12h), vitamin K (Konaktion, Hoffmann-La Roche, Basel, Switzerland, 1 mg/kg, SC, q24h), lactulose (Laevolac, Fresenius Kabi, Graz, Austria, 5 mL, PO or per rectum, q8h), famotidine (Famotidine, West-Ward, Eatontown, NJ, USA, 1 mg/kg, IV, q24h), SAME (SAM-e, Jarrow Formulas, Los-Angeles, CA, USA, 100mg, PO, q12), thiamine (Bevitine,

Cenexi, Fontenay sous Bois, France, 70 mg, SC, 24h), mannitol (20% Osmitol, Baxter, Deerfield, IL, USA, 0.5 g/kg, Slow IV, PRN, based on the attending clinician decision). Seizure activity was controlled with phenobarbital (Luminal, Kern Pharma, Barcelona, Spain, 2.5 mg/kg IM, q12h) and propofol (Lipuro 1%, B. Braun, Melsungen, Germany, 2 mg/kg, slow IV PRN).

During the second day of hospitalization, the cat was accidentally overdosed with phenobarbital, at 25mg/kg IM, raising concern due to the presumptive PSS, which was hypothesized to result in a very slow metabolism of the drug, lead to severe phenobarbital toxicity and further neurological deterioration of this cat, which presented with severe CNS impairment.

As phenobarbital concentration could not have been measured immediately, hemodialysis was elected, attempting to enhance drug clearance. The initial serum phenobarbital concentration (1 hr post injection) was 35.5  $\mu$ g/mL (the therapeutic phenobarbital range for treating epilepsy is 10-30  $\mu$ g/mL). Intermittent 4-hour hemodialysis treatment (AK 200™ S dialysis machine, Gambro, Unterschleissheim, Germany, F3 dialyzer, Fresenius Medical Care AG &CO. KGaA, Bad Homburg, Germany) was performed, and a total of 10.08 liters of blood were dialyzed. Two hours into the hemodialysis treatment, serum phenobarbital concentration was 10.6  $\mu$ g/mL. Post-hemodialysis phenobarbital (after 4 hours of treatment) concentration was 5.2  $\mu$ g/mL. Although serum phenobarbital concentration has improved over time, the cat remained in stupor for 18 hours post dialysis, and had several convulsion episodes. With no neurological improvement, the owners elected euthanasia, but declined necropsy. Serum phenobarbital concentration at this time was 5.1  $\mu$ g/mL.

## DISCUSSION

This report demonstrates, for the first time, to the best knowledge of the authors, the utility of hemodialysis in managing phenobarbital toxicosis in a cat. The cat in the present case was tentatively diagnosed with PSS with convulsions, and phenobarbital was administered as anticonvulsant, to alleviate seizure activity (3,4). The recommended phenobarbital dose for cats with generalized seizures is 2-4 mg/kg every 8 to 24 hours (3,4), while this cat was accidentally administered 25 mg/kg IM. This dose is not expected to be toxic in a cat with normal liver function. However, in this cat, with PSS and abnormal liver function test results, this high dose

raised concern that phenobarbital may not be metabolized effectively by the liver and its associated side-effects might be detrimental. Therefore dialytic intervention was elected.

Barbiturates are barbituric acid derivatives, and are classified based on their pharmacokinetic properties into long-acting and short-acting agents (and further classified into ultrashort-, short-, and intermediate-acting agents) (5). The effective duration of action of each barbiturate is related to its unique structure. Short-acting barbiturates are more protein bound and lipid soluble, and have a more rapid onset, higher pKa, and shorter duration of action, and are metabolized almost exclusively by the liver (5-9). Long-acting barbiturates have less tissue accumulation (and low volume of distribution [VDS]), are less lipid soluble, and in addition to being metabolized by the liver, the active drug is readily excreted as an active drug by the kidneys (6,7). Hepatic metabolism, the main endogenous clearance path of all barbiturates, induces the hepatic cytochrome P450 enzymatic system, which accelerates the metabolic clearance of cytochrome P450 substance (5). The reported oral LD<sub>50</sub> of phenobarbital in cats is 125mg/kg (10), and the drug has a low safety margin (therapeutic dose may reach 50-70% of the LD<sub>50</sub>) (11, 12). The toxic effects of phenobarbital are exerted mainly on the CNS, pulmonary and cardiovascular systems (13). The onset of clinical signs depends on the exposure route and the barbiturate type involved. At lower doses, barbiturates mainly affect the CNS, inducing sedation and hypnosis. Symptoms of a moderate overdose usually include sluggishness, lack of coordination, and drowsiness. At higher doses, barbiturates suppress the medullary respiratory center and chemoreceptors, inducing respiratory depression and shallow respiration and coma occurs in severe poisoning (13). These effects are more severe in cats, in which the control of respiratory activity is believed to be more complex compared to other species (12), as the reticular formation governs the medullary control of respiration. Aspiration pneumonia, associated with respiratory depression, is another cause of death following barbiturate overdose (14,15). Cardiovascular depression might be a consequence of medullary vasomotor centers depression. Vascular tone and contractility are compromised at higher doses, which may cause hypotension. Moreover, the effect of barbiturates on sodium, potassium and calcium concentration in cardiac myocytes might adversely affect cardiac contractility (12).

The methods to enhance phenobarbital clearance in

human patients include dopamine-induced diuresis, forced alkaline diuresis, multiple activated charcoal doses, and application of extracorporeal treatments, such as charcoal hemo-perfusion or haemodialysis (16-21). Although cases of phenobarbital overdose treated successfully by hemodialysis have been reported in humans, there is a lack of consensus whether hemodialysis is superior to hemoperfusion in treating barbiturate overdose.

A number of factors should be considered before determining whether a drug can be effectively eliminated by hemodialysis or by hemoperfusion (22). Hemodialysis is most effective when a substance has low molecular weight (<500 D), high water solubility, minimal protein binding and low VDS. Hemo-perfusion enhances the clearance of highly protein bound molecules, by adsorption. Phenobarbital has a low molecular weight (232 D), a relatively low VDS (0.54-0.9 L/kg body weight), but is 40-60% protein bound (23). The previous assumption that hemo-perfusion is superior to hemodialysis was based on comparison of the former with hemodialysis using low-efficiency dialyzers and low blood flow rates (24). The introduction of high-efficiency dialyzers calls for a reevaluation of this assumption, and hemodialysis should be considered as the main treatment option for phenobarbital overdose. *In vitro* experiments have demonstrated that there are no significant differences in the phenobarbital clearance using dialysis, when the drug was in plasma or in a protein-free solution (25). In this cat, the phenobarbital concentration reduction ratio over the treatment period was 85%, indicating drug elimination was effective, even if a low efficiency dialyzer is used, as in this case. Although the present cat had relatively low serum phenobarbital concentration, this case demonstrates that despite the VDS of phenobarbital and its moderate binding to plasma protein, it can be effectively eliminated even using a low efficiency dialyzer.

In retrospect, there was probably no need in this case to enhance phenobarbital clearance by using extracorporeal treatment, as its serum concentration one hour after its accidental overdose was close to its therapeutic range. However, the drug's serum concentration were available much later, as its measurements were done by a referral laboratory, and unavailable to the attending clinicians in real time. The decision to use hemodialysis, with a low efficiently dialyzer, rather than hemo-perfusion, was influenced by the patient's size, in order to minimize the extracorporeal circuit volume.

In summary, this report describes an accidental phenobarbital overdose in a cat with a putative PSS, treated successfully by hemodialysis with a low efficiency dialyzer, and has led to a significant decrease in serum phenobarbital concentration within a relatively short time.

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