Evaluation of Transdermal Administration of Phenobarbital in Healthy Cats

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ABSTRACT

The purpose was to determine the safety and achievable serum concentrations of transdermally administered phenobarbital in healthy cats. The hypothesis was that transdermal phenobarbital would achieve therapeutic serum concentrations (15–45 μg/mL) with minimal short-term adverse effects. Enrolled cats had normal physical and neurologic exams and unremarkable bloodwork. Transdermal phenobarbital in a pluronic lecithin organogel–based vehicle was administered at a dosage of 3.0–3.1 mg/kg per ear pinna (total of 6.0–6.2 mg/kg) every 12 hr for 14 days. Serum phenobarbital concentrations were measured 3–6 hr after dosing at seven different times over 15 days. The mean and median serum concentration of phenobarbital at study completion were 5.57 and 4.08 μg/mL, respectively. Mean peak concentration and mean time to peak concentration were 5.94 μg/mL and 13.3 days, respectively. Mild adverse effects were observed. Potency was analyzed in three replicates of the transdermal phenobarbital gel administered; potencies ranged from 62.98 to 82.02%. Transdermal application of phenobarbital in healthy cats achieves a detectable, but subtherapeutic, serum concentration and appears safe in the short term. The use of therapeutic drug monitoring is recommended when this formulation of phenobarbital is used to ensure therapeutic serum concentrations are achieved. (*J Am Anim Hosp Assoc* 2019; 55:1–7. DOI 10.5326/JAAHA-MS-6670)

Introduction

Seizure disorders are a well-recognized neurological problem in cats, and seizures are one of the most common forms of neurological disease in this species.[1–4] One retrospective study from the Clinic of Small Animal Medicine, Department of Veterinary Clinical Sciences, Ludwig-Maximilians-Universität, showed the incidence of seizures in cats evaluated at their hospital over a 5 yr period to be 2.1%.[5] The most frequent cause of seizures in dogs is idiopathic epilepsy, whereas cats are more likely to have an underlying cause for seizures (e.g., structural brain disease or toxic or metabolic abnormalities).[5–7]

Phenobarbital is a barbiturate that is a well-established anticonvulsant for the treatment of seizure disorders in veterinary medicine, regardless of the underlying cause. It is often considered a first-line treatment for canine and feline seizures and by many the drug of choice for cats.[3] Both parenteral and oral formulations are available for administration in cats, and there are well-established pharmacokinetic studies for oral and intravenous administration of phenobarbital in cats.[8,9] Phenobarbital is metabolized by the liver and has an elimination half-life of 34–43 hr in cats.[8,9] The recommended starting dose is 1.5–2.5 mg/kg bodyweight, orally every 12 hr. Serum phenobarbital concentrations reach steady state at 10–14 days after initiation of oral administration and should, therefore, be evaluated every 10–14 days following any alteration in dose. A recent retrospective study showed that seizure control was

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CBC (complete blood count); PLO (pluronic lecithin organogel)

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achieved in most cats with a serum phenobarbital concentration between 15 and 45 μg/mL, regardless of the cause of the seizures.[10] Adverse effects associated with phenobarbital use in cats include sedation, ataxia, paraparesis, and weight gain secondary to polyphagia, polydipsia, and polyuria.[1,11] Hepatotoxicosis, a well-recognized complication in dogs on phenobarbital, has not been reported in cats.[11–13] Other adverse effects that are rarely reported include leukopenia and thrombocytopenia, as well as immune-mediated hypersensitivity reactions (severe cutaneous eruptions and lymphadenopathy). All of these adverse effects are typically reversible following discontinuation of phenobarbital.[14,15] Adverse effects tend to be more severe at the beginning of treatment and at higher doses.[11]

Although oral administration of phenobarbital is an effective means of achieving therapeutic serum concentrations, it can be difficult for owners to medicate their cats long-term. Difficulty arises in administering oral medications consistently in cats because of demeanor and attitude. Advantages of using transdermal drug delivery include bypassing the gastrointestinal tract and hepatic first-pass metabolism, control of absorption, and the availability of multiple sites for application.[16] An additional advantage in cats specifically is the avoidance of oral administration, which many times is not tolerated. Potential disadvantages of transdermal drug delivery include localized cutaneous reactions, lack of bioavailability, and the greater time required for drug absorption. An additional potential disadvantage is increased or inadvertent drug exposure to owners or other animals; the use of nonpermeable gloves during application of the drug is required.[16,17] To the authors' knowledge, no studies have specifically evaluated owner compliance with oral phenobarbital administration in cats. However, a retrospective study evaluating population characteristics of cats with hypertrophic cardiomyopathy found that owners had compliance issues with oral medications 21.5% of the time medication was administered, making it a more common problem than adverse drug reactions.[18] With phenobarbital, there may be an increase in the likelihood of poor seizure control if drug doses are missed. Situations also occur in which humane euthanasia is elected because of an inability to orally medicate cats with seizure disorders. Identification of a route of administration better tolerated by cats would be highly advantageous. The use of transdermal phenobarbital in cats would improve owner compliance, minimize stress among the patient population, and improve therapeutic efficacy, which may help avoid humane euthanasia.

Transdermal medications have undergone limited studies in veterinary medicine to determine efficacy and safety, but many agents are used empirically.[16] Studies performed in cats evaluating several transdermal formulations of medications have shown varying efficacy.[19–32] A recently published study evaluated the application of transdermal phenobarbital at different dosages and in different vehicles in cats. The results of this study showed that therapeutic phenobarbital levels can be achieved in cats with a pluronic lecithin organogel (PLO) vehicle.[33] Additional studies are necessary to confirm if these findings are repeatable and if results are the same when the medication is produced in other compounding manufacturers.

The objectives of the present study were to determine if transdermal administration of phenobarbital could achieve therapeutic serum concentrations in cats and to monitor for any signs of adverse effects. The hypothesis was that transdermal phenobarbital would achieve therapeutic serum concentrations with minimal short-term adverse effects, placing it under consideration to become an anticonvulsant formulation to treat seizure disorders in cats.

Materials and Methods

Patient Selection

Six healthy, male and female, client-owned, indoor cats, between 1 and 15 yr of age and weighing between 3.0 and 6.0 kg, were enrolled in this study. Cats were included regardless of their neuter status. Health was determined on the basis of results of a physical examination, neurological examination, complete blood count (CBC), chemistry, bile acids assay, total T4, and Feline Immunodeficiency Virus/Feline Leukemia Virus test[a]. The cats had no known prior significant medical problems and were not currently on any medications. The sample size for this study was accordant with standard protocol for descriptive pharmacokinetic studies in dogs.[34,35] No power calculation was necessary because descriptive statistics were used.

Transdermal Formulation Dosing

The transdermal phenobarbital was obtained from a nationally advertised compounding pharmacy in a PLO-based vehicle. The concentrations of phenobarbital within the transdermal formulation ranged from 120 to 180 mg/mL. The concentrations were based on the bodyweight of each cat to allow 0.1 mL to be applied to the inner pinnae of each ear *q* 12 hr for 14 days. This volume would deliver a desired dosage of 3.0–3.2 mg/kg per ear (total of 6.0–6.4 mg/kg per cat *q* 12 hr). This dose was based on data obtained from an initial pilot study previously performed at the Washington State University Veterinary Teaching Hospital In this pilot study, transdermal phenobarbital was applied to one healthy cat to determine appropriate dosing, blood sampling frequency, and duration of dosing period. Standard oral dosing of 15 mg (2.5 mg/kg) *q* 12 hr was used; therapeutic concentrations were reached in this cat. We increased the total dose for our prospective study from the pilot to

ensure we would reach therapeutic levels in all cats. The transdermal phenobarbital formulation was supplied in 1 mL syringes, which allowed accurate dosing of 0.1 mL per pinna per application. Owners were instructed by the primary investigator on the appropriate application of the formulation with a gloved finger based on a previously reported technique.[25,26,31,36] Owners were also instructed to remove any remaining grossly apparent medication with a gloved finger prior to a new application.

Sample Collection and Analysis

All blood sampling and repeat examinations were performed at the Washington State University Veterinary Teaching Hospital. Between sampling and examinations, cats were kept in their home environment without restrictions to their normal activities. Serum was obtained, and phenobarbital concentrations measured at 3–6 hr after dosing on days 3, 5, 7, 9, 11, 13, and 15. Neurologic and physical examinations were performed prior to each blood draw. Repeat hematologic and serum biochemical analyses, including bile acids testing, were performed at the completion of the study at the Washington State University College of Veterinary Medicine Clinical Pathology Laboratory. Plasma samples were stored at –80°C for subsequent analysis of serum phenobarbital concentrations at the North Carolina State University College of Veterinary Medicine Pharmacology Laboratory.

Starting at day 0, aliquots of the phenobarbital formulations for cats 4–6 were stored at –80°C for subsequent potency analysis at the North Carolina State University College of Veterinary Medicine Clinical Pharmacology Laboratory. A solid-phase competitive chemiluminescent enzyme immunoassay was used to determine phenobarbital concentrations.

Monitoring for Adverse Effects

Monitoring for short-term adverse effects was accomplished by repeating physical and neurological examinations on the cats immediately prior to each blood draw. Both pinnae were examined by one of the investigators (D.P.K., S.A.T., A.V.C.) prior to blood sampling. Any cutaneous reactions at the site of administration of the formulation were noted and recorded. Digital photographs of the pinnae were also taken prior to the start of the study and at each recheck examination by the investigators (D.P.K., S.A.T., A.V.C.). Adverse systemic and metabolic effects were monitored via repeat CBC, chemistry, and bile acids assay performed at the end of the dosing period (day 15). At study completion, owners were sent a questionnaire. They were questioned regarding any changes in their cat's appetite, attitude, behavior, urination, and defecation while at home during the study. Owners were asked if they would prefer a transdermal formulation to an oral formulation (liquid/tablet/capsule) when medicating their cat in the future. They were also asked if daily application of phenobarbital subjectively affected normal interactions between them and their cat or the human–animal bond.

Data Analysis

Descriptive statistics were used to analyze the data. The mean, median, and standard deviation of phenobarbital serum concentrations were determined at day 15, as well as means and standard deviations for peak serum concentration and time to peak serum concentration. The potencies of the transdermal formulations for cats 4–6 were also determined. Adverse effects noted on physical/neurologic examinations, found on serial photographs of the pinnae, and described by owners while in the home environment were reported. Any abnormalities found on repeat blood work were also reported.

Results

Six healthy cats were included in the study. These included four domestic shorthair cats and two domestic medium hair cats. Three were neutered males and three were spayed females. Initial physical exams were normal for all cats, with the exception of cat 5 having mild mucopurulent discharge from the left nostril. Initial neurologic examinations were normal for each cat. CBC and biochemistry results were unremarkable for cats 1–4. Cat 5 had a mild increase in alanine aminotransferase (102 U/L; reference 17–90 U/L) and mild hyperglobulinemia (5.3 g/dL; reference 2.7–5.1 g/dL). Cat 6 had a mild hyperglobulinemia (5.7 g/dL; reference 2.7–5.1 g/dL). Bile acids (pre- and postprandial) and total T4 were normal for all cats, and Feline Immunodeficiency Virus/Feline Leukemia Virus tests were negative for all cats.

The mean (standard deviation) and median phenobarbital concentrations at day 15 were 5.57 μg/mL (3.16 μg/mL) and 4.08 μg/mL, respectively. Data for serum phenobarbital concentrations for each cat are listed in **Table 1** and **Figure 1**. Mean peak concentration (standard deviation) and mean time to peak concentration (standard deviation) were 5.94 μg/mL (3.11 μg/mL) and 13.3 days (2.1 days), respectively.

None of the cats developed significant adverse effects during the study, and all six were able to complete the 2 wk course of phenobarbital. CBC and biochemistry results performed at the completion of the study were unremarkable for cats 1, 2, 3, and 5. Cat 4 had a mild elevation in alanine aminotransferase (95 U/L; reference 17–90 U/L). Cat 6 had a persistent mild hyperglobulinemia (5.7 g/dL; reference 2.7–5.1 g/dL). All cats had normal pre- and postprandial bile acids. The pinnae of two cats (cats 1 and 2) developed mild erythema during the course of the treatment (**Figure 2**) but did not necessitate discontinuation of application of phenobarbital. Cat

TABLE 1

Phenobarbital Formulation Concentrations and Serum Phenobarbital Concentrations at Day 15

Cat	Sex	Age, yr	Weight, kg	Dose Administered, mg/kg/ear	Mean Potency, %	Concentration of Transdermal Formulation	Day 15 Serum Concentration, μg/mL
1	CM	3	5.8	3.1	NA	180	4.29
2	SF	2	4.0	3.0	NA	120	11.68
3	SF	4	4.0	3.0	NA	120	7.64
4	CM	1	4.6	3.0	75.72	140	2.84
5	CM	15	5.7	3.0	64.41	170	3.08
6	SF	6	3.8	3.2	79.43	120	3.86

Sex, age, weight, dose of transdermal phenobarbital administered per ear, concentration of transdermal phenobarbital formulation and serum concentration of phenobarbital at study completion for all six cats enrolled in the study.
CM, castrated male; NA, not available; SF, spayed female.

6 was noted to have a small excoriation of the left pinna adjacent to the application site that was presumed to be self-inflicted. This excoriation was mild, did not progress, and did not necessitate exclusion from the study. No measures, such as placement of an Elizabethan collar, were necessary to prevent further disturbance of the pinna. This area of excoriation was avoided with future applications of phenobarbital. Cat 5 had intermittent mucopurulent discharge from the left nostril during the course of the study similar to presentation. Cat 5 also had one day of diarrhea on day 13 of application. Cat 3 was noted by the owner to be polydipsic/polyuric on days 11–13 of application. No abnormalities were found on serial neurologic examinations. Inspection of the pinnae during the course of the study commonly showed a dried and flakey appearance to the medication following application (Figure 2).

Three replicates of the transdermal phenobarbital gel administered to cats 4–6 were analyzed for potency. The formulation for cat 4 was labeled as 140 mg/mL and found to have a mean potency of 75.72% (reference 74.76–76.50%). The formulation for cat 5 was labeled as 170 mg/mL and found to have a mean potency of 64.41% (reference 62.98–66.37%). The formulation for cat 6 was labeled as 120 mg/mL and found to have a mean potency of 79.43% (reference 76.83–82.02%).

In a questionnaire sent to owners at the conclusion of the study, three out of six responded. All three owners felt their cats tolerated the medication without any adverse effects. Two owners indicated they would prefer transdermal over oral medications for ease of application. One owner preferred oral versus transdermal but still felt that most owners would find transdermal medications easier to administer. One owner felt there was a change in normal interactions between them and their cat during the study. This owner commented that the cat would hide when approached, but the owner felt as if the same behavior would have been displayed with oral medications. No other concerns were reported.

Discussion

The results of this prospective study show that transdermal application of phenobarbital in healthy cats in a PLO vehicle achieves a detectable, but subtherapeutic, serum concentration. All of the cats

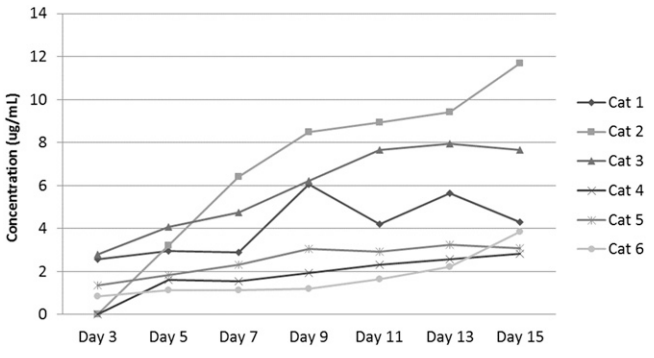

FIGURE 1 *Serum phenobarbital concentrations for each of the six cats enrolled in the study at various points in time.*

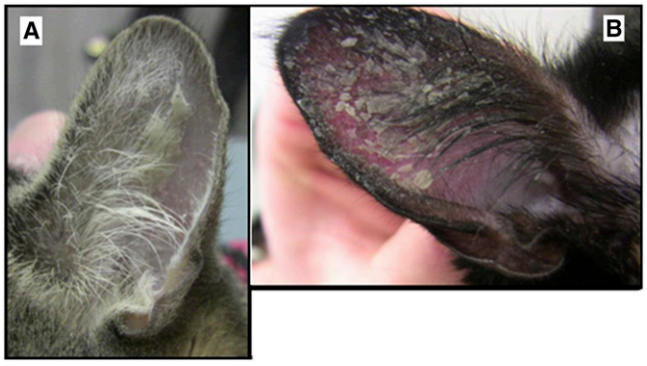

FIGURE 2 *Pinnae of cats 4 (A) and 6 (B) following transdermal phenobarbital application.*

in this study failed to achieve a target therapeutic range of 15–45 μg/dL.[10] The formulation was safe and well tolerated in the short term.

The primary challenge in the development of transdermal agents is identifying compounds with the appropriate chemical characteristics to be absorbed through the skin. Difference in skin structure and function between veterinary species is also a compounding challenge. The efficacy of a topical agent is primarily dependent upon the barrier properties of the skin, as well as the ratio of the area of the applied medication to the species' total body mass.[37] The *stratum corneum* (outermost layer of the epidermis) is the primary barrier to chemical penetration; in humans, the skin can absorb drugs at an estimated maximum rate of only 1 mg/cm^2.[37] It is not known how this translates to veterinary medicine. However, for cats with a limited surface area for absorption (e.g., pinna of the ear), this limits the maximum dose that can be administered and excludes application of certain drugs that require higher dosage (e.g., antibiotics).[38] We attempted to overcome this limitation by applying phenobarbital to both pinnae twice daily to increase the overall surface area. We also increased the total dose applied to each pinna (3–6 mg/kg) after our initial pilot study to increase the concentration gradient at the skin with the goal of improving absorption.

The physicochemical characteristics of a transdermal agent also impact absorption. Ideal compounds have a low molecular weight, are lipophilic, are soluble in oil and water, and have a high partition coefficient and melting point.[16] One in vitro study evaluated the physiochemical properties of phenobarbital; the drug was shown to have attributes that would make it a candidate for transdermal administration.[39] Additionally, the drug must also be soluble in the vehicle in which it is delivered.[37,38] Drugs have been formulated with vehicles or "penetration enhancers" to facilitate transport across skin (e.g., lecithin, isopropyl palmitate, and poloxamers that act as surfactants and emulsifiers).[38] They primarily exert their effect by causing increased fluidity in the intercellular lipids of the stratum corneum and cause stratum corneum cells to swell and/or leach out structural components. This leads to enhanced drug penetration because the stratum corneum is the primary barrier to drug absorption. PLO acts as an emulsifying agent and allows formation of a drug in a gel matrix. It is the most common transdermal vehicle, making it an appropriate choice for use in this study.[16] However, this particular vehicle may have been inappropriate and led to poor absorption of phenobarbital. Additional commercially available vehicles (e.g., Lipoderm) require further investigation to determine their usefulness. A recent study published in 2015 found that when phenobarbital was formulated in a Lipoderm vehicle and administered transdermally at 9 mg/kg *q* 12 hr, only low therapeutic levels were reached.[33]

A possible explanation for failure to reach therapeutic levels in our study was the consistency of the formulations. The formulation was dry and brittle (Figure 2) rather than of gel consistency. The consistency of the formulation applied during our pilot study (a PLO gel obtained from the same pharmacy as the medication used in this prospective study) was that of a gel, which differed significantly from the dry consistency of the formulations used in this prospective study. This led to difficulty in applying the allotted dose to each pinna as well as the ability of the formulation to remain in contact with pinna surface for extended periods of time. The dry consistency of the medication made repeatable application of the medication challenging, with all owners commenting that the medication was difficult to apply and that it commonly fell off of the pinna soon after application. It is vital that transdermal medications remain in contact with the skin to exert their effect; the primary driving force for diffusion of a substance across the stratum corneum and into the epidermis is the concentration gradient created by application of a substance to the skin.[37] Owner compliance did not appear to be a factor in the obtained subtherapeutic drug levels in these cats. All owners were instructed on how to appropriately apply the medication at study commencement; they were also given a schedule to record when doses were administered.

As previously stated, a major limitation with transdermal medications is unpredictability in the consistency, potency, and stability of the formulations between batches and pharmacies. All formulations were compounded with PLO gel and were obtained from the same commercial pharmacy. Not only was consistency different between the pilot and prospective study cats, but the potency was also quite varied. The range of potency in the three formulations for which potency was assessed ranged from 62 to 82% of the listed concentration. The fact that the actual potency was much lower than the stated potency resulted in a lower administered dose and, therefore, blunted the peak serum phenobarbital concentrations achieved. Unfortunately, we only obtained potency information for the formulation used in cats 4–6. The data from these cats was obtained following data collection and analysis from cats 1–3. After obtaining subtherapeutic serum levels of phenobarbital in cats 1–3, it became prudent to determine the potency of the medication used on the second set of cats studied. There may be inconsistent concentrations of phenobarbital within each tube, which could account for the extreme lack of correlation between the applied dose and the serum phenobarbital concentration. We did not evaluate the stability of these formulations over time but all were administered within the expiration date of the formulation, 4 wk from date of order. However, it is possible potency may have decreased over the duration of the study.

A previous study by Delamaide Gasper et al. showed that a PLO gel at 9 mg/kg twice daily did reach therapeutic serum

concentrations.[33] In this study, when a dose of 3 mg/kg was given *q* 12 hr, therapeutic levels were not reached. The dose used in our study was 6 mg/kg *q* 12 hr; this lower dose may have been a reason therapeutic serum concentrations were not reached. However, the cat used in our pilot study was given a dose of 15 mg (2.5 mg/kg *q* 12 hr), and therapeutic concentrations were reached in this cat. It may be that that consistency and potency of the formulation, rather than dose, resulted in subtherapeutic serum concentrations in this prospective study. In the Delamaide Gasper study, transdermal formulations were custom-made specifically for the study at a noncommercial compounding pharmacy, whereas we used a commercial compounding pharmacy for our formulations.[33] We chose to use a commercial compounding pharmacy in order to better reflect the situation most epileptic cats would experience if prescribed transdermal phenobarbital. Another potential cause of disparate results from the Delamaide Gasper study and ours is that potency studies were not performed on formulations in the Delamaide Gasper study. It is possible that the transdermal phenobarbital formulations used in that study were more potent, and thus cats received doses greater than 12 mg/kg, thereby generating higher serum concentrations.

Adverse effects were also evaluated in our study. Transdermal phenobarbital appeared to be well tolerated and safe in the short term among the study population. Only minor adverse effects were noted, with irritation of the pinna being most common. There is a possibility that we may have seen more signs of sedation and polydipsia/polyuria if high serum concentrations had been achieved, but we expect that these adverse effects would be mild, similar to those observed in cats receiving oral phenobarbital long term.[11]

The brief questionnaire sent to owners at the conclusion of the study was meant to subjectively gauge owner satisfaction with administration of a transdermal medication. Responses were obtained from half of the owners included in the study. Most owners indicated they would prefer to administer a transdermal formulation rather than an oral medication to their cat in the future.

Conclusion

In conclusion, transdermal phenobarbital in a PLO gel acquired from a commercial compounding pharmacy achieved detectable, but subtherapeutic, serum concentrations in cats and appeared safe in the short term. It seems unlikely that this particular formulation would be a viable anticonvulsant option for cats with seizures. Transdermal phenobarbital can be considered for select feline patients, but caution must be taken with regard to the formulation used. The authors strongly recommend the use of therapeutic drug monitoring when transdermal phenobarbital is used to ensure that therapeutic serum concentrations are achieved. Future studies are necessary to investigate additional vehicles and formulations that may allow enhanced transdermal absorption of phenobarbital in cats.

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FOOTNOTES

[a] Snap Feline Immunodeficiency Virus/Feline Leukemia Virus Combination Test; IDEXX Laboratories, Westbrook, Minnesota

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